# DEVELOPMENT AND *IN-VITRO* DISSOLUTION STUDIES OF BILAYER TABLET OF METOPROLOL SUCCINATE (SR) AND HYDROCHLOROTHIAZIDE (IR)

Dissertation

Submitted in partial fulfillment of the requirement for the

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**IN**

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**OF**

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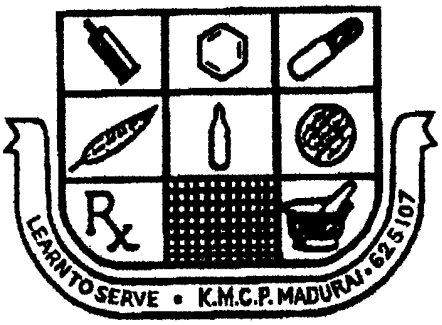
**CHENNAI.**




**DEPARTMENT OF PHARMACEUTICS**

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## CERTIFICATE

This is to certify that the dissertation entitled "**DEVELOPMENT AND IN VITRO DISSOLUTION STUDIES OF BILAYER TABLET OF METOPROLOL SUCCINATE (SR) AND HYDROCHLOROTHIAZIDE (IR)**" submitted by **Mr. RAMAN. TATIVAKA** to The Tamilnadu Dr.M.G.R.Medical University, Chennai, in partial fulfillment for the award of Master of Pharmacy in Pharmaceutics at K.M. College of Pharmacy, Madurai, is a bonafide work carried out by him under my guidance and supervision during the academic year 2011-2012.

**GUIDE & PRINCIPAL**

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## CONTENTS PAGE NO

# INTRODUCTION

## 1. TABLETS [1, 2]:

Tablets fall in the category of solid dosage forms each containing a single dose of one or more active ingredients and usually obtained by compressing uniform volume of particles, some are prepared by molding. Most tablets are intended for oral route. The rest are through sublingual, buccal or vaginal.

**Advantages of tablets:**

- Packaging in blister packs can also enhance the stability of tablets.
- Compared to liquid dosage forms chemically and physically stable.
- Low manufacturing cost.
- They provide a content variability.
- Easy to package and ship.
- Simple to identify.
- Manufacturing process and techniques can provide tablets special properties say enteric coatings.

**Disadvantages of tablets:**

- Some drug resists compression in to tablet.
- Difficulty in swallowing in some patients; pediatrics and geriatrics.
- Poor bioavailability of poorly soluble drugs or poorly absorbable drugs.
- Some drugs may cause local irritation effect harm GI mucosa.
- In emergency cases, intravenous or intramuscular injections are more effective.

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The objective of the design and manufacture of the compressed tablet is to deliver orally, the correct amount of the drug in the proper form, at or over the proper time and in the desired location, and to have its chemical ingredients projected to the point. In tablets with smaller dosages a good weight variation does not ensure good content uniformity, but a large weight variation precludes a good content uniformity.

To assure uniform potency for tablets of low dose drugs, a content uniformity tests applied. In this test 30 tablets are randomly selected for the sample and at least 10 of

them are assayed individually. Nine of the 10 tablets must contain not less than 85% or more than 115% of the labeled drug content. The tenth tablet may not contain less than 75% or more than 125% of the label content. If these conditions are not met, the tablets remaining from the 30 must be assayed individually and one may fall out side 85% to 115%

**2. What is Bi-layer Tablet?**

A tablet with two mutually exclusive layers, represented by two clearly different colors, provided manufacturers with a way to produce a product that looked more interesting than a standard white pill.

**Bilayer Tablets – Why special technology is required? [3]**

For a variety of reasons: patent extension, therapeutic, marketing to name a few. To reduce capital investment, quite often existing but modified tablet presses are used to develop and produce such tablets. This explains why the development and production of quality bi-layer tablets needs to be carried out on purpose-built tablet presses to overcome common bi-layer problems, such as layer--separation, insufficient hardness, inaccurate individual layer weight control, cross-contamination between the layers, reduced yield, etc. Using a modified tablet press may therefore not be your best approach to producing a quality bi-layer tablet under GMP-conditions. Especially when in addition high production output is required.

To produce a quality bi-layer tablet, in a validated and GMP-way, it is important that the selected press is capable of:

- Preventing capping and separation of the two individual layers that constitute the Bi-layer tablet
- Providing sufficient tablet hardness
- Preventing cross-contamination between the two layers
- Producing a clear visual separation between the two layers
- High yield
- Accurate and individual weight control of the two layers.

**Reasons for the use of bilayered tablet design [4]:**

- Bilayered tablets are preferred when the release profiles of the drugs are different from one another i.e.. in the present case Hydrochlorothiazide has to be released immediately and Metoprolol succinate has to be released sustainably.
- These provide a unique presentation and identification for the product in the market for that manufacturer.
- For stagged drug release IR and SR in the same tablet.
- For chronic condition requiring repeated dosing.
- To co-administered two different drugs in the same dosage forms.
- To minimize the physical and chemical incompatibilities.

**3. According to method of manufacturing:**

**a) Compressed tablet:**

It is obtained by compressing uniform volume of particles using "Tablet compression machine". It is used for large scale production.

**b) Molded tablet:**

Molding means shaping and hardening of semi solid mixture of drug and excipients. It is obtained using "Tablet mold". It is restricted for small-dose tablet and small scale production.

**4. TABLET EXCIPIENTS:**

The tablet is composed of the drug together with various excipients. These are biologically inert ingredients which either enhance the therapeutic effect or necessary to conduct the tablet.

**a) Fillers:** or diluents are a bulking agent, providing a quantity of material which can accurately be formed in to a tablet.

Examples are lactose or sorbitol.

**b) Binders:** These are holding the ingredients together so that they form a tablet.

Examples are Methyl cellulose or gelatin.

c) **Lubricants:** These are added to reduce the friction between the tablet and the punches and dies so that the tablet compression and ejection processes are smooth.

Examples are magnesium stearate or polyethylene glycol.

d) **Disintegrants**: These are used to promote wetting and swelling of the tablet so that it breaks up in the gastro intestinal tract; this is necessary to ensure dissolution of the API.

Examples are starch or cellulose

e) **Super disintegrants:** These are sometimes used to greatly speed up the disintegration of the tablet.

Additional ingredients may also be added such as colorants, flavoring agents and coating agents.

## 5. ORAL DRUG DELIVERY [2]:

Most conventional oral drug products, such as tablets and capsules, are formulated to release the active drug immediately after oral administration, to obtain rapid and complete systemic drug absorption. Such immediate release products result in relatively rapid drug absorption and onset of accompanying pharmacodynamic effects. However, after absorption of the dosage form is complete, plasma drug concentration decline according to drug's pharmacokinetic profile. Eventually, plasma drug concentration fall below the minimum effective plasma concentration (MEC), resulting in loss of therapeutic activity. Before this point is reached, another dose is usually given if a sustained therapeutic effect is desired. An alternative to administering another dose is to use a dosage form that will provide sustained drug release, and therefore maintain plasma drug concentrations, beyond what is typically seen using immediate- release dosage forms.

**6. MODIFIED DRUG DELIVERY:**

The term modified-release drug product is used to describe products that alter the timing and/or the rate of release of the drug substance. A modified-release dosage form is defined as one for which the drug-release characteristics of time course and/or location are chosen to accomplish therapeutic or convenience objectives not offered by conventional dosage forms such as solutions, ointments, or promptly dissolving dosage forms as presently recognized. Several types of modified-release drug products are recognized.

**6.1 Modified release delivery systems may be divided conveniently in to four categories:**

A. **Delayed release**
B. **Controlled release**
    i. **Sustained release**
    ii. **Extended release**
C. **Site specific targeting**
D. **Receptor targeting**

**A. Delayed Release:**

These systems are those that use repetitive, intermittent dosing of a drug from one or more immediate release units incorporated in to a single dosage form.

Examples of delayed release systems included repeat action tablets, capsules and enteric-coated tablets where timed release is achieved by barrier coating.

**B. Controlled release systems:**

These systems include any drug delivery systems that achieves slow release of drug over an extended period of time and also can provide some control, where this be of a temporal or spatial nature, or both, of drug release in the body, or in other words, the system is successful at maintaining constant drug levels in the target tissue or cells.

i) **Sustained release:**

These systems include any drug delivery system that achieves slow release of drug over an extended period of time.

ii) **Extended release:**

Pharmaceutical dosage forms that release the drug slower than normal manner and necessarily reduce the dosage frequency by two folds.

**C. Site specific targeting:**

These systems refer to targeting of a drug directly to a certain biological location. In this case the target is adjacent to the effected organ or tissue.

**D. Receptor targeting:**

These systems refer to targeting of a drug directly to a certain biological location. In this case the target is the particular receptor for a drug with in organ or tissue.

Site specific targeting and receptor targeting systems satisfy the spatial aspect of drug delivery and are also considered to be controlled drug delivery systems.

## 7. EXTENDED RELEASE CONCEPT [7]:

Over the past 30 years as the expenses and complications involved in marketing new drug entities have increased. With concomitant recognition if the therapeutic advantages of extended drug delivery, greater attention has been focused on development of extended or controlled release drug delivery systems. The attractiveness of these dosage forms is due to awareness to toxicity and other properties of drugs when administered or applied by conventional method in the form of tablets, capsules, injectables, ointments, etc. Usually conventional dosage forms produce wide range fluctuation in drug concentration in the blood stream and tissues with consequent undesirable toxicity and poor efficiency. The factors such as repetitive dosing and unpredictable absorption led to the concept of extended drug delivery systems.

**Advantages of extended release drug delivery:**

- Reduced frequency of drug.
- Improved patient compliance.

- Reduced blood level oscillation characteristic of multiple dosing of conventional dosage forms.
- Reduced amount of drug administration.
- Maximum availability with a minimum dose.
- Control of drug absorption, high blood level peaks that may be observed after administration of high availability drug can be reduced.
- Safety margin of high potency drugs can be increased.
- Incidence of both local and systemic adverse effects can be reduced.
- Increased reliability of therapy.

**Disadvantages of extended release drug delivery:**

- Administration of sustained release medication does not prompt termination of therapy.
- The physician has less flexibility in adjusting dosage regimen.
- Sustained release forms are designed for the normal population.

**8. IMMEDIATE RELEASE CONCEPT:**

The tablet is intended to be released rapidly after administration, or the tablet is dissolved and administered, as solution.

It is most common type and includes:

- ❖ Disintegrating tablet
- ❖ Chewable tablet
- ❖ Sublingual tablet
- ❖ Buccal tablet
- ❖ Effervescent tablet

**9. MATRIX TABLETS[8]:**

A matrix is a uniform mixture of drug, excipients and polymer that is homogenously fixed in a solid dosage form.

Matrix devices consist of drug dispersed homogenously throughout a polymer matrix. In the model, drug in the outside layer exposed to the bathing solution is

dissolved first and then diffuses out of the matrix. This process continues with the interface between the bathing solution and the solid drug moving toward the interior. For this system rate of dissolution of drug particles within the matrix must be much faster than the diffusion rate of the dissolved drug leaving the matrix.

This system involves the following assumptions:

- A pseudo steady state is maintained during drug release.
- The diameter of the drug particles is less than the average distance of drug diffusion through the matrix.
- The diffusion coefficient of drug in the matrix remains constant i.e., no change occurs in the characteristics of the polymer matrix.

- The mechanism of release from these systems can be considered in two ways:
  a) Extraction of the medicament by a simple diffusion process through enveloping homogenous matrix.
  b) Leaching of the medicament by the bathing fluid, which is able to enter the drug-matrix please through pores, cracks and inter granular spaces.

**Table: Materials used as retardants in Matrix tablet formulations**:

| Sl. No | Matrix characteristics | Materials |
|---|---|---|
| **1.** | Insoluble, Inert | Polyeythylene, polyvinyl chloride, Methylacrylate Co-polymer, Ethyl cellulose |
| **2.** | Insoluble, Erodible | Carnauba wax, stearyl Alcohol, Stearic acid, PEG |
| **3.** | Hydrophilic | Methyl cellulose, HPMC, sodium CMC. |

## 10. HYPERTENSION:

Blood pressure is usually classified based on the systolic and diastolic blood pressures. Systolic blood pressure is the blood pressure in vessels during a heart beat. Diastolic blood pressure is the pressure between heartbeats. A systolic or the diastolic blood pressure measurement higher than the accepted normal values for the age of the individual is classified as prehypertension or hypertension.

Hypertension has several sub-classifications, including hypertension stage I, hypertension stage II, and isolated systolic hypertension. Isolated systolic hypertension refers to elevated systolic pressure with normal diastolic pressure and is common in the elderly. These classifications are made after averaging a patient's resting blood pressure readings taken on two or more office visits. Individuals older than 50 years are classified as having hypertension if their blood pressure is consistently at least 140 mmHg systolic or 90 mmHg diastolic. Patients with blood pressures higher than 130/80 mmHg with concomitant presence of diabetes mellitus or kidney disease require further treatment.

Hypertension is also classified as resistant if medications do not reduce blood pressure to normal levels.

### 10.1 SIGNS AND SYMPTOMS [9, 10]:

**Accelerated hypertension**

Accelerated hypertension is associated with headache, drowsiness confusion, vision disorders, nausea, and vomiting. These symptoms are collectively called hypertensive encephalopathy Hypertensive encephalopathy is caused by severe small blood vessel congestion and brain swelling which is reversible if blood pressure is lowered.

**Secondary hypertension**

Some additional signs and symptoms suggest that the hypertension is caused by disorders in hormone regulation. Hypertension combined with obesity distributed on the trunk of the body, accumulated fat on the back of the neck ('buffalo hump), wide purple marks on the abdomen (abdominal striae), or the recent onset of diabetes suggests that an

individual has a hormone disorder known as Cushing's syndrome. Hypertension caused by other hormone disorders such as hyperthyroidism, hypothyroidism, or growth hormone excess will be accompanied by additional symptoms specific to these disorders. For example, hyperthyroidism can cause weight loss, tremors heart rate abnormalities, reddening of the palms, and increased sweating Signs and symptoms associated with growth hormone excess include coarsening of facial features, protrusion of the lower jaw, enlargement of the tongue, excessive hair growth, darkening of the skin color and excessive sweating. Other hormone disorders like hyperaldosteronism may cause less specific symptoms such as numbness, excessive urination, excessive sweating, electrolyte imbalances and dehydration, and elevated blood alkalinity and also cause mental pressure.

**Medications:**

Several classes of medications, collectively referred to as antihypertensive drugs are currently available for treating hypertension. Reduction of the blood pressure by 5 mmHg can decrease the risk of stroke by 34%, of ischaemic heart disease by 21%, and reduce the likelihood of dementia heart failure. and mortality from cardiovascular disease. The aim of treatment should be to reduce blood pressure to <140/90 mmHg for most individuals, and lower for individuals with diabetes or kidney disease (some medical professionals recommend keeping levels below 120/80 mmHg). If the blood pressure goal is not met, a change in treatment should be made as therapeutic inertia is a clear impediment to blood pressure control. Co morbidity also plays a role in determining target blood pressure, with lower BP targets applying to patients with end-organ damage or proteinuria.

The first line antihypertensive supported by the best evidence is a low dose thiazide-based diuretic.

Often multiple medications are needed to be combined to achieve the goal blood pressure. Commonly used prescription drugs include: ACE inhibitors, alpha blockers, angiotensin II receptor antagonists beta blockers, calcium channel blockers

diuretics (e.g. hydrochlorothiazide), direct rennin inhibitors and Glyceryl trinitrates which has the activity of vasodilatation, thus controlling high blood pressure.

Some examples of common combined prescription drug include:

A fixed combination of an ACE inhibitor and a calcium channel blocker. One example of this is the combination of perindopril and amlodipine. The efficacy of which has been demonstrated in individuals with glucose intolerance or metabolic syndrome..

Combinations of an ACE-inhibitor or angiotensin II–receptor antagonist, a diuretic and an *NSAID* (including selective COX-2 inhibitors and non-prescribed drugs such as ibuprofen) should be avoided whenever possible due to a high documented risk of acute renal failure.

**11. β -blockers [12]:**

**β-blockers** or beta-adrenergic blocking agents, beta-adrenergic antagonists, beta-adrenoreceptor antagonists or beta antagonists, are a class of drugs used for various indications. They are particularly for the management of cardiac arrhythmias, cardio protection after myocardial infarction (heart attack), and hypertension.

**Indications for beta blockers include:**

- Angina pectoris
- Atrial fibrillation
- Cardiac arrhythmia
- Congestive heart failure
- Essential tremor
- Glaucoma
- Hypertension
- Migraine prophylaxis
- Mitral valve prolapse
- Myocardial infarction
- Phaeochromocytoma, in conjunction with α-blocker
- Postural orthostatic tachycardia syndrome
- Symptomatic control (tachycardia, tremor in anxiety and hyperthyroidism).

**11.1 Beta blockers have also been used in the following conditions:**

- Acute aortic dissection
- Hypertrophic obstructive cardiomyopathy
- Marfan syndrome (treatment with propranolol slows progression of aortic dilation
- and its complications)
- Prevention of variceal bleeding in portal hypertension
- Possible mitigation of hyperhidrosis
- Social anxiety disorder and other anxiety disorders

**12. Congestive heart failure:**

Although beta blockers were once contraindicated in congestive heart failure as they have the potential to worsen the condition, studies in the late 1990s showed their efficacy at reducing morbidity and mortality in congestive heart failure. Bisoprolol, carvedilol and sustained-release metoprolol are specifically indicated as adjuncts to standard ACE inhibitor and diuretic therapy in congestive heart failure.

Beta blockers are primarily known for their reductive effect on heart rate, although this is not the only mechanism of action of importance in congestive heart failure. Beta blockers, in addition to their sympatholytic B1 activity in the heart, influence the rennin/angiotensin system at the kidneys. Beta blockers cause a decrease in rennin secretion, which in turn reduce the heart oxygen demand by lowering extracellular volume and increasing the oxygen carrying capacity of blood. Beta blockers sympatholytic activity reduces heart rate, thereby increasing the ejection fraction of the heart despite an initial reduction in ejection fraction.

# LITERATURE REVIEW

- **Gurvinder**[17] ***et al.,*** examined the influence of critical formulation and processing variables as described in the AAPS/FDA Workshop II reporter on scale-up of oral extended-release dosage forms, using a hydrophilic polymer hydroxypropyl methylcellulose (Methocel K100 LV). Granulation (1.5 Kg, 3000 units) were manufactured using a fluid-bed process, lubricated and tablets (100 mg metoprolol tartrate) were compressed on an instrumented Manesty D3B rotary tablets press. Dissolution tests were performed using USP apparatus 2, at 50 rpm in 900 ml phosphate buffer (pH6.8).

- **Al-Saidana** [18] ***et al..,*** carried out pharmacokinetic evaluation of oral controlled release formulation (guar gum-based three layer matrix tablets) containing highly soluble metoprolol tartrate has a model drug. The plasma concentration of metoprolol tartrate was estimated by reverse-phase HPLC. The pharmacokinetic parameters were calculated from the plasma concentration of metoprolol tartrate versus time data. The delayed $T_{max}$ lower $C_{max}$ decreased un altered bioavailability and prolonged indicated a slow and prolonged release of metoprolol tartrtate from guar gum three-layer matrix tablets in comparison with the immediate release tablet dosage form.

- **Bjoern**[19] ***et al..,*** investigate the effects of beta 1-blockade on left ventricular (LV) size and function for patients with chronic heart failure. Large-scale trials have shown that a marked a decrease in mortality can be obtained by treatment of chronic heart failure with beta-adrenergic blocking agents. Possible mechanisms behind this effect remain yet to be fully elucidated. In this randomized, placebo-controlled and double-blind study to the metoprolol CR/XL randomized intervention trial in Heart Failure (MERIT-HF).

- **Narendra**[20] **a** ***et al.,*** evaluated the effect of formulation variables on release properties and bio-adhesive strength in development of three layered buccal compact containing highly water-soluble drug metoprolol tartrate (MT) by statistical optimization

technique. Formulations were prepared based on rotatable central composite design with peripheral polymer ratio (carbopol 934 P HPMC 4KM) and core polymer ratio (HPMC 4KM:sodium alginate) as two independent formulation variables. The three layered buccal compact comprises peripheral layer, core layer and backing layer. Four dependent (response) variables were considered: bio-adhesion force, percentage MT release at 8h, T 50% (time taken to release 50% of drug) and release exponent (n). The release profile data was subjected to curve fitting analysis for describing the release mechanism of MT from three layered buccal compact. The main effect and interaction terms was quantitatively evaluated by quadratic model. The decrease in MT release was observed with an increase in both the formulation variable and as the carbopol:HPMC ratio increases the bio-adhesive strength also increases.

- **Jozesef**[21] ***et al.,*** investigated the drug release and FT-IR characteristics of metolose patches the changes of metolose SM 4000 (methylcellulose) and metolose 90SH (hypromellose) proportions. FT-IR spectroscopy measurements were performed in parallel with the metoprolol tartrate release study to track the effect of the composition on the drug release. Linear relationship was found with good correlation between the logarithm of time interval necessary to release 63.2% of metoprolol tartrate (dvalues) and the peak area measured within the characteristic FT-IR wavenumbers of patches.

- **Milton**[22] ***et al.,*** indicated carvedilol exerts multiple antiadrenergic effects in addition to β1receptor blockade, the recently completed carvedilol or metoprolol europian trial (COMET), which showed that carvedilol ( 25 mg twice daily) reduced mortality by 17% when compared with metoprolol ( 50 mg twice daily ), a result that was consistent with the differences seen across earlier controlled trials with β blockers in survivors of an acute myocardial infarction and in patient with chronic heart failure. These analyses suggest that the observed difference in the mortality effects of metoprolol and carvedilol is not related to a difference in the magnitude or time course of their β1 blocking effects but instead reflect antiadrenergic effects of carvedilol in addition to β1 blockade.

- **Alan**[23] ***et al.,*** used extended Cox regression to examine the association between receipt of different blockers and risk of readmission for HF after adjustment for potential confounders. During follow-up, there were 3,234 person-years of exposure to blockers (39.3% atenolol, 42.0% metoprolol tartrate, 12.3% carvedilol, and 6.4% other). Crude 12-month rates of readmissions for HF were high overall (42.6 per 100 person-years). After adjustment for potential confounders, cumulative exposure to each blockers, and propensity to receive carvedilol compared with atenolol, adjusted risks of readmission were not significantly different for metoprolol tartrate (adjusted hazard ratio 0.95, 95% confidence interval 0.85 to 1.05) or for carvedilol (adjusted ratio 0.92, 95% confidence interval 0.74 to 1.14).

- **Alaa**[24] ***et al.,*** presented different spectrophotometric and HPTLC densitometric for the simultaneous determination of lisinopril and hydrochlorothiazide in pharmaceutical tablets.

- **Hillaert**[25] ***et al.,*** studied the capability of the capillary zone electrophoretic (CZE) and micellar electrokinetic capillary chromatographic (MEKC) methods to simultaneously separate hydrochlorothiazide and six angiotension–II- receptor antagonists (ARA–II): candesartan, eprosartan mesylate, irbesartan, losartan potassium, telmisartan, and valsartan. The CZE and MEKC methods are suitable for the qualitative and quantitative determination of combined HCT/ARAΠs in pharmaceutical formulations. Depending on the ARA–II at least one of the two methods can be used for each combination.

- **Ndindayino**[26] ***et al.,*** evaluated the bioavailability of hydrochlorothiazide (HCT) from moulded isomalt–based tablets after oral administration of 50 mg HCT as an oral moulded tablet and as a lozenge, in comparison with a conventional tablet formulation. The relative bioavailability of the moulded tablet administered as a lozenge and as an oral tablet was 106.29, 30.9% and 89.49, 25.9%, respectively, in relation to the conventional tablet formulation.

- **Sam**[27] ***et al..,*** studied the influence of different formulation and process parameter on the characteristics of lyophilized oral dosage forms. Maltodextrins, gelatins, xanthan gum and hydroxyethylcellulose were evaluated as excipient in the formulation of freeze-dried tablets. The resulting were analysed for mechanical strength, porosity, disintegration time and residual moisture. Scanning electron micrographs of the fracture plane of the tablets were taken. Additionally dissolution tests were performed on lyophilized tablets containing hydrochlorothiazide as a model drug.

- **S. Mohamed Halith**[28] ***et al.,*** Formulated and evaluated of bilayer tablets of amlodipine besilate and metprolol succinate and have done on DSC studies formulation and compare to pure compound Heat flow rates were measured over a temperature range of 30°C - 300°C at a heating rate of 15°C/min for Amlodipine Besilate pure drug, placebo and tablet samples. Similarly temperature range of 25°C- 250°C at a heating rate of 5°C/min was used for Metoprolol Succinate pure drug, placebo, and tablet samples.

- **Vaijanath G**. [29] ***et al.,*** Simultaneous determined metoprolol succinate and amlodipine besylate in pharmaceutical dosage form by HPLC. The mobile phase consisting of buffer (aqueous triethylamine pH 3) and acetonitrile in the ratio of 85: 15 (v/v) at a flow rate of 1.0 ml/min was used. The method was validated according to the ICH guidelines with respect to specifity, linearity, accuracy, precision and robustness.

- **Vishnu P.Choudhari**[30] ***et al.,*** compared i*n vitro*, newly formulated controlled-release tablets with standard commercial tablets (MetXL50).The prepared matrix tablets showed good mechanical properties (hardness and friability). Hydroxypropyl methyl cellulose and Alginate-based tablet formulations showed high release-retarding efficiency, and good reproducibility. FTIR study suggesting that HPMC K15M and Alginate are good candidates for preparing modified release tablet formulations Metoprolol succinate.

- **Prasada Rao**[31] ***et al.,*** developed a simple, rapid and selective HPLC method developed for quantization of Amlodipine Besylate and Metoprolol succinate from bulk drug and

pharmaceutical formulations using a mobile phase consisting mixture of 0.02 M phosphate buffer solution and Acetonitrile as 80:20 at the flow rate of 1 mL/min. An Inertsil ODS-CV column was used as stationary phase. The retention time of Amlodipine Besylate and Metoprolol succinate were 3.92 and 10.43 respectively.

- **Brijesh**[32] ***et al,*** developed a simple, sensitive and rapid reverse phase HPLC method for the simultaneous analysis of metoprolol succinate and hydrochlorothiazide in a solid dosage form. The drugs were analysed by a reverse phase C-18 column using 50mM di-sodium hydrogen phosphate:methanol:acetonitrile in a ratio of 525:225:250 as mobile phase. The flow rate was 1 ml/min and the compounds were detected by a UV-detector at 222 nm at a column temperature of 24 ± 2 ºC. The method was statistically validated for linearity and accuracy.

- **R. K. Seshadri**[33] ***et al.,*** developed simple ultra performance liquid chromatographic (UPLC) method developed for the simultaneous estimation of Metoprolol (MT), Atorvastatin (AT) and Ramipril (RM) from capsule dosage form. The (4.6 mm x 50 mm, 1.8 µm) column with a mobile phase consisting of 0.06% ortho phosphoric acid in water having an ion pair reagent, 0.0045 M Sodium lauryl sulphate as buffer, at ratio of buffer. Acetonitrile (50:50 v/v), at 55°C column temperature with a flow rate of 1.0 ml/min. The method was found to be rugged and robust and can be successfully used to determine the three drugs and its combinations.

- **V.Rajamanickam**[34] ***et al.,*** developed and validate a economic, rapid reversed-phase high-performance liquid chromatographic method for the quality control of Metoprolol succinate and amlodipine besylate in pharmaceutical preparations with lower solvent consumption along with the short analytical run time leads to an environmentally friendly chromatographic procedure that allows the analysis of a large number of samples in a short period of time.

- **N.N.Rajendran**[35] ***et al.,*** investigated the effect of a novel drug- drug solid dispersion approach on the dissolution of hydrochlorothiazide in a fixed dose combination with Losartan potassium Solid dispersions by differential scanning calorimetry, x-ray diffractometry and dissolution tests and the results were compared with that of pure

drugs and physical mixtures. Solid dispersion as well as physical mixture were then compressed into tablets and evaluated for physicochemical, stability and dissolution characteristics and the results compared with commercial tablets.

- **Rekha Gangola**[36] ***et al.,*** studied the combination of Hydrochlorothiazide and Telmisartan is useful in treatment of mild to moderate hypertension, and is well tolerated with a lower incidence of cough than ACE inhibitors. The marketed tablets contain Telmisartan and Hydrochlorothiazide in ratio of 40:12. The widespread use of these drugs in combination, necessitates development of analytical methods for their simultaneous estimation. Several analytical procedures have been proposed for the quantitative estimation of Telmisartan and Hydrochlorothiazide separately and in combination with other drugs.

- **Padma priya S**[37] ***et al.,*** prepared solid dispersions in proportions similar to commercial preparations of hydrochlorothiazide and captopril (HCT-CAP) combination. The solid dispersions were evaluated for *in vitro* dissolution characteristics and the results were compared with that of physical mixtures of HCT-CAP and pure hydrochlorothiazide. The dissolution rate of hydrochlorothiazide from solid dispersions was found to be faster than that of physical mixtures and pure drug.

- **Messerli**[38] ***et al.,*** evaluated the antihypertensive efficacy of hydrochlorothiazide (HCTZ) by ambulatory blood pressure (BP) monitoring. Fourteen studies of HCTZ dose 12.5 to 25 mg with 1,234 patients and 5 studies of HCTZ dose 50 mg with 229 patients fulfilled the inclusion criteria. The antihypertensive efficacy of HCTZ in its daily dose of 12.5 to 25 mg as measured in head-to-head studies by ambulatory BP measurement is consistently inferior to that of all other drug classes. Because outcome data at this dose are lacking,

- **D.E. Clarke**[39] ***et al.,*** studied the acute and chronic effects of hydrochlorothiazide on adrenergic neuronal and receptor function in the isolated perfused dog mesenteric arteries have been characterized. Hydrochlorothiazide, 2.7 mg/min for 90 min, perfused directly into the arteries, failed to alter adrenergic mechanisms. Chronic oral treatment of dogs with hydrochlorothiazide, 10 mg/kg/day, for 6 months enhanced the frequency-

response curve to periarterial nerve stimulation without affecting the vasoconstrictor responses to norepinephrine.

- **S. G. Chrysant[40] *et al.,*** reported on long-term efficacy, safety, and tolerability data from this third-year extension trial in which patients received the combination of valsartan 80 mg and Hydrochlorothiazide 12.5 or 25 mg for at least 2 years.

- **M. Lusina[41] *et al.,*** investigated how the quality of a drug product changes with time under the influence of environmental factors, to establish a shelf life for the product and to recommend storage conditions of Hydrocholorothiazide tablets, OPA/Al/PVC//Al blisters were found to provide adequate protection for the product. Based on the first 12 months of the formal stability study, a shelf life of 24 months. Losartan/hydrochlorothiazide tablets in OPA/Al/PVC//Al blisters are demonstrated to be chemically, physically and microbiologically stable.

- **D.S. Desai,[42] *et al.,*** studied hydrochlorothiazide (HCTZ) drug substance is known for its excellent solid-state stability, it can undergo hydrolysis with the formation of formaldehyde and 4-amino-6-chloro-l,3 benzenedisulfonamide (free amine). The degradation of HCTZ in a dosage form is undesirable due to the tight limits that need to be set for the free amine content. It was hypothesized that the mechanism of degradation of HCTZ in the presence of PVP and/or Pluronic ® F68 was due to solubilization of the HCTZ by these excipients in the moisture present in tablets, followed by its hydrolysis.

- **Y.S.R. Krishnaiah[43] *et al.,*** designed oral controlled drug delivery systems for highly water-soluble drugs using guar gum as a carrier in the form of a three-layer matrix tablet of Metoprolol tartrate. Matrix tablets containing either 30 (M1), 40 (M2) or 50% (M3) of guar gum by wet granulation technique using starch paste as a binder. Three-layer matrix tablets of metoprolol tartrate by compressing on both sides of guar gum matrix tablet granules of metoprolol tartrate M1, M2 or M3 with either 50 (TL1M1, TL1M2 or TL1M3) or 75 mg (TL2M1, TL2M2 or TL2M3) of guar gum granules as release retardant layers. Both the matrix and three-layer matrix tablets were evaluated for hardness, thickness, drug content uniformity, and subjected to in vitro drug release

studies. The guar gum, in the form of three-layer matrix tablets, is a potential carrier in the design of oral controlled drug delivery systems for highly water-soluble drugs such as metoprolol tartrate.

- **Mothilal M[44] *et al.,*** formulated ODDS for metoprolol Succinate using different concentrations of mannitol, by wet granulation technique. The tablets were coated by dip coating with cellulose acetate. Stainless steel drill pins were used to make an orifice on the tablets. Tablet thickness, hardness, weight variation and drug content analysis, drug release study were performed. Orifice diameter was examined using scanning electron microscopy (SEM). With increase in osmogen content and bore size, rate of drug release were found to be increasing an optimum concentration of osmogen and bore size to give a zero order release was identified.

- **Alexander[45] *et al.,*.** evaluated and compared the in-vitro and in-vivo erosion profiles of two tablet formulations primarily consisting of hydroxypropylmethylcellulose (HPMC) and lactose. HPMC polymer percolation threshold in controlled release matrix formulations: 20 and 40% (w/w). In-vitro erosion behavior was studied using traditional gravimetric and scintigraphic methods, with radiolabel led charcoal used as a marker to quantify erosion profiles in scintigraphic studies. Tablets containing 40% (w/w) HPMC (polymer level above percolation threshold) demonstrated robust in-vivo performance and showed stronger correlation with in-vitro erosion profiles. The matrix formulation with a lower concentration of HPMC and higher lactose concentration is more likely to perform poorly in the in-vivo environment.

- **Chuan-Yu[46] *et al.,*** described the compaction behavior of binary mixtures and bilayer tablets of two common pharmaceutical excipients, microcrystalline cellulose and lactose. The delamination phenomena during the manufacturing of bilayer tablets and fracture patterns of tablets subjected to diametrical compression are examined using X-ray computed to monography. The mechanical properties of binary and bilayer tablets of the same composition were also determined and compared.

- **Jakkie**[47] ***et al.,*** reported the effect of V-mixer size on the mixing of magnesium stearate with directly compressible microcrystalline cellulose and evaluated the mixing process and compare the performance of the mixers, the extent of the decrease in tablet crushing strength was measured. The kinetics of the decrease in crushing strength were best described by the sum of two separate processes, one first-order and the other second-order. Overall, the faster second-order process dominated mixing because the first-order rate decreased, while the second-order rate increased. with an increase in mixer volume. Results showed that the limiting crushing strength increased with an increase in mixer size and that there was a linear relationship between the limiting crushing strength and the logarithm of the volume of the mixer. A decrease in mixer load from 33 to 18% also led to an decrease in tablet strength.

- **Jenny Herder**[48] ***et al.,*** studied the properties of the granules and the tablets fall into two groups according to whether the molecular weight of the polymer is high or low. The granules of low molecular weight were smaller and more compact, with better flow properties but with less tensile strength of the compacts, whereas the opposite was valid for granules of high molecular weight. The explanation for these differences is linked to the proposed granulation mechanism of HPMC, in which the properties of the gel layer are important. The dominant factors governing the properties are the molecular weight and, to lesser extent, the degree of substitution.

- **Calum**[49] ***et al***., developed bilayer mucoadhesive tablets of Nicotine evaluated to determine the suitability of the formulation as a Nicotine replacement product to aid in smoking cessation. A combination of 20% w/w carbopol 934 and 20% w/w Hydroxypropylcellulose was found to provide suitable adhesion and controlled drug release. The formulation of bilayer tablet containing the adhesive controlled release layer and a fast releasing layer provided an initial burst release of drug followed by the controlled release for a period of upto 4 hours.

- **Miyazaki**[50] ***et al*.,** developed potential of bilayer tablets containing 1:4, 1:1 and 4:1 weight ratios of pectin and HPMC for the sustained release of Diltiazem by sublingual

administration has been investigated. An *in vitro* sustained release of Diltiazem over 5 hours was achieved with bilayer tablets composed of a drug-free ethyl cellulose layer in addition to the pectin/HPMC layer containing drug. Bioavailability of Diltiazem was 2.5 times than achieved by oral administration for single layer tablets and 1.8 time for the bilayer tablets.

- **Anil Chaudhary[51] *et al.,*** prepared microporous bilayer osmotic tablet bearing dicyclomine hydrochloride and diclofenac potassium by using a new oral drug delivery system for colon targeting. The tablets were coated with microporous semi permeable membrane and enteric polymer using conventional pan-coating process. The number of pores was dependent on the amount pore former in the semi permeable membrane. *In vitro* dissolution results indicated that system showed acid resistance, timed release was able to deliver drug at an approximate zero order up to 24 hour.

- **Carmen[52] *et al.,*** prepared new buccal delivery devices comprising a drug containing mucoadhesive layer and a drug free backing layer, by two different methods. The mucoadhesive layer was composed of a mixer of drug and chitosan, with or without an anionic cross linking polymer (polycarbophill, sodium alginate, gellan gum), and the backing layer was made of ethyl cellulose. The double layered structure design was expected to provide drug delivery in a unidirectional fashion to the mucosa and avoid loss of drug due to wash out with saliva. Using nifedipine and propranolol hydrochloride as slightly and highly water soluble model drugs, respectively, it was demonstrated that show promising potential for use in controlled delivery of drugs to the oral cavity. The uncrosslinked chitosan containing devices absorbed a large quantity of water, jelled and then eroded allowing drug release. The bilaminated films shows a sustained drug release in a phosphate buffer (pH 6.4)

- **Yong[53] *et al.,*** used electrochemically synthesized conducting polymer polypyrrole (PPy) film on gold electrode surface was used as a novel support for bilayer lipid membrane (BLMs). The formation of PPy supported bilayer lipid membranes (s-BLMs) is dependent on the chemical structure of the lipid use.

- **Mina**[54] ***et al.*** developed a gastro retentive controlled release drug delivery system with swelling, floating and adhesive properties by using hydroxyl propyl methyl cellulose (HPMC K15M) and/or sodium alginate (Na alginate) as release-retarding polymer(s) and sodium bicarbonate ($NaHCO_3$) or calcium carbonate ($CaCO_3$) as a gas former. Swelling ability, floating behavior, adhesion period and drug release studies were conducted in 0.1N HCl (pH 1.2) at 37±0.5˚C.

- **Panagiotis barmpalexis**[55] ***et al.,*** investigated nimodipin-polyethylene glycol solid dispersions for the development of effervescent controlled release floating tablet formulation.

- **Fridrun Podczecka**[56] ***et al.,*** determined the tensile strength of bilayer tablets made from different grades of microcrystalline cellulose. While these grades are chemically identical, they differ significantly in their particle size distribution and in their mechanical properties such as young's modules of elasticity. Both particle size and Young's modules of elasticity influenced the overall strength of layered tablets. If the material forming the lower layer was more elastic, then the beam strength was reduced due to tension introduced into the system, acting especially at the layer interface and potential causing partial or complete delamination.

- **Hema**[57] ***et al.,*** described a modulated release, multiunit oral drug delivery technology using a system based on ionic interactions of anions of salts with quaternary ammonium ions of the ammoniomethacrylate polymer. The system consisted of a drug layered, EUDRAGIT NE-coated salt core which was further coated with EUDRAGIT RS. The relative effects of different anions on the polymer permeability have been investigated by studied their influence on the in vitro drug release. A prototype formulation of metoprolol succinate using this technology was developed and the drug release from the formulation was adjusted to have a release profile which would match the circadian rhythm i.e a higher amount of drug would be available after an initial lower release (accelerated type of release).

- **Jeffrey[58] *et al.,*.** studied Beta blockers which are known to suppress renin release in hypertension and in patient taking angiotensin converting enzyme (ACE) inhibitors. The effect of additional blockade on neurohumoral modulation in patients with severe heart failure (HF) who received ACE inhibitors.

- **Yogesh[59] *et al.,*** investigated the effect of molecular characteristic co polymers viz pluronic P103, P123, and F127 on micellar behavior and solubilisation of a diuretic drug, hydrochlorothiazide (HCTZ), the critical micellization temperatures (CMTs) and size for empty as well as drug loaded miscells are reported. The CMTs and miscells depended on the hydrophobicity and molecular weight of the copolymer; a decrease in CMT and increase in size was observed on solubilization. The solubilization of the drug hydrochlorothiazide (HCTZ) in the block copolymer nano aggregates at different temperatures (28, 37, 45˚ C), pH (3.7, 5.0, 6.7) and in the presence of added salt (NaCl) was monitored by using UV-Visble spectroscopy and solubility data were used to calculate the solubilization characteristics; micelle water partition coefficient (P) and thermodynamic parameters of solubilization viz. Gibbs free energy (Gs˚), enthalpy (Hs˚), and entropy (Ss˚). The solubility of the drug in copolymer increases with trend: P103> P123> F127.

- **Ajit Kulkarni[60] *et al.,*** Developed of regioselective bilayer floating tablets of Atenolol and Lovastatin for biphasic release profile. In DSC studies the tablet was ground to powder and a 1-2 mg sample was hermetically sealed in an aluminum pan and heated at a constant rate of 10°C/min, over a temperature range of 50-200 °C. Inert atmosphere was maintained by purging nitrogen gas at a flow rate of 20 ml/min.

- **Sapna N[61] *et al.,*** studied once daily sustained release tablets of venlafaxine, a novel antidepressant, to know the extended release tablet from time of administration.

- **Velasco-De-paola[62] *et al.,*** studied dissolution kinetics of controlled-release tablets containing Propranolol Hydrochlororide. The physical properties of the tablets were determined. Dissolution tests were performed in capsules containing the raw material

using the following dissolution media: (A) distilled water, (B) simulated gastric juice without enzymes, and (C) simulated enteric juice without enzymes. A dissolution test was also performed for simulated samples (tablets) using distilled water as the dissolution medium.

- **Gummudavelly Sandeep[63] *et al.,*** studied extended release or controlled release formulation are its ability to maintain ß1 selectivity over 24hours, but with relative lack of peak plasma concentration, thus avoiding decreased clinical ß 1 selectivity as seen at high plasma concentration. Release kinetics evaluated by using USP-22 (Paddle) dissolution apparatus. In-vitro release study showed that ERT10 for 25mg label claimed were well suited to extend release for 20 hours with zero order release. In-vitro swelling studies revealed by Korsmeyer-Peppa's model that, the drug release governed by swelling of polymer and it is anomalous diffusion or non-fickian transport.

- **A. Streubel[64] *et al.,*** developed new multi-layer matrix tablets to achieve bimodal drug release profiles (fast release /slow release / fast release). Hydroxypropyl methylcellulose acetate succinate (HPMCAS, type MF) as a matrix former, because it is water-insoluble at low, and water-soluble at high pH values. The addition of a fourth, drug-containing and fast disintegrating initial dose layer yielded the desired bimodal drug release patterns. The process and formulation parameters affecting the resulting release rates using theophylline and acetaminophen as model drugs.

- **K.G. Wagner[65] *et al..,*** studied enteric coated bisacodyl pellets were compressed into divisible disintegrating tablets on a high speed rotary tablet press. The degree of pellet damages was examined via the bisacodyl dissolution during the acid treatment of' the drug release test for enteric coated articles according to USP. The damages depended on the type of ®ller-binder used and settings of the tablet press. Avicel PH 101 proved to be the most suitable ®ller-binder, effecting homogeneous distribution of the pellets within the tablets, as could be shown by image analysis of coloured pellets. Reducing the proportion of pellets to 60% per tablet, less than 10% of bisacodyl were released within 2 h during acid treatment thus full flling the requirements of the USP.

- **Rashmi Dahima**[66] ***et al.*** increased the solubility and dissolution rate of amlodipine besylate by the preparation of its solid dispersion with cross povidone using solvent evaporation method. Drug polymer interactions were investigated using differential scanning calorimetry (DSC) and Fourier transform infrared spectroscopy (FTIR). Surface morphology of solid dispersion particle determined by SEM study. Dissolution rate of solid dispersion was determined in 0.01 N HCl at 75 rpm. The obtained results showed that dispersion of the drug in the polymer considerably enhanced the dissolution rate. It revealed that crosspovidone in solid dispersion itself act as superdisintegrant and binder and an optimum concentration of a pregelatinized starch is required for obtaining rapidly disintegrating tablets. The potential of experimental design in understanding the effect of the formulation variables on the quality of mouth dissolving tablets containing solid dispersion of a hydrophobic drug.

- **Naeem**[67] ***et al*.,** developed and characterized bilayer tablet formulations of tramadol HCl (TmH) and acetaminophen (AAP) microparticles. Coacervation via temperature change the encapsulated method used for the preparation of the microparticles, with ethyl cellulose (EC) of medium viscosity as the polymer for extending drug release. FTIR, XRD, DSC and TGA data for the formulations indicate good compatibility and stability. Furthermore, accelerated stability studies confirmed the stability of the formulations. Controlled drug release from the microparticles and bilayer tablets was observed for 8 h and 12h, respectively. Microencapsulated TmH and AAP can be developed into suitable bilayer tablets that are stable and capable of releasing the drugs over 12h.

- **L. Yang**[68] ***et al.,*** formulated components were poly(ethylene oxide) (PEO), lactose, and theophylline. Results indicate that the formulation of each layer and the combined triple-layer tablet exhibited similar compression behavior, and the consolidation mechanism was shown to follow predominantly plastic deformation as evidenced by the shape of Heckel plots and high SRS (Strain Rate Sensitivity) values. A triple-layer tablet formulation necessitates careful selection of plastic, brittle, and other desirable components to ensure comparable compactibility profiles.

- **Rakhee A. Surana[69] *et al*.,** formulated Phenyl propanolamine Hydrochloride sustained release pellets. Uni Glatt fluid bed processor (Glatt, Germany) was used for drug solution layering and also for sustained release coating.By using Hypromellose E5, Ethylcellulose 10cps and Ethylcellulose 45cps polymers in combination. Polymeric solution was prepared by dissolving polymers into different solvents in different proportion to form clear coating solution. The pellets were evaluated for appearance, shape and size analysis, density, assay, content uniformity, in-vitro drug release studies, stability study and kinetic study. The optimized batches were charged for stability at 40°C and 75% RH for 2 months. The drug release studies were repeated after storage for 2 months at conditions like room temperature (RT) and 40ºC and 75% RH.

## Aim of the present investigation

The present investigation relates to the development of Bilayer dosage form containing combination of sustained and immediate release layer by using Metoprolol Succinate and Hydrochlorothiazide respectively for the treatment of Hypertension.

Metoprolol Succinate is a beta selected adrenoreceptor blocking agent, for oral administration in the treatment of hypertension, anginapectoris and heart failure. It has a half life of 3 to 7 hours. Metoprolol reduces the force of contraction of heart muscle and there by lowers blood pressure. By reducing the heart rate and the force of muscle contraction, Metoprolol reduces the need for oxygen by heart muscle. Heart pain (angina pectoris) occurs when oxygen demand of the heart muscle exceeds the supply of oxygen, the reducing the demand for oxygen, is helpful in treating heart pain.

Metoprolol Succinate extended-release tablet is a beta-1 (cardio-selective) adrenoceptor-blocking agent formulated to provide controlled and predictable release of metoprolol. Hydrochlorothiazide (HCT) is a well-established diuretic and antihypertensive agent, which promotes natruresis by acting on the distal renal tubule.

Hydrochlorothiazide is a first line diuretic drug of the thiazide class that acts by inhibiting the kidney's ability to retain water. This reduces the volume of the blood, decreasing lower peripheral vascular resistance.

The combination product more effective than monotherapy with the individual components but the combination product allows a low-dose multidrug regimen as an alternative to high-dose monotherapy, thereby, minimizing the likelihood of dose-related side-effects

The purpose of this study was to develop a bilayer tablet of sustained release of Metoprolol Succinate using Hydroxy propyl methyl cellulose as hydrophilic polymer and immediate release of Hydrochlorothiazide Direct compression method.

Finally intra batch reproducibility and stability study to be carried out for the selected bilayer tablets.

**4. Plan of work**

**1. Preformulation study**:

1.1 Raw material analysis of Metoprolol Succinate.

1.2 Raw material analysis of Hydrochlorothiazide.

1.3 Drug –Excipient compatibility studies.

1.4 Physical observation.

1.5 FT-IR.

**2. Formulation and evaluation of Bilayer tablets:**

2.1 Formulation of sustained release granules of Metoprolol Succinate.

2.2 Formulation of Immediate-release granules of Hydrochlorothiazide.

2.3 Evaluation of sustained release granules of Metoprolol Succinate.

2.4 Evaluation of immediate release granules of hydrochlorothiazide.

2.5 Compression of bilayer tablets.

2.6 Evaluation of compressed Bilayer tablets.

2.7 Packing of Bilayer tablets (Blister packing).

**3. Optimized formulation was subjected to the following studies:**

3.1 Release kinetic study for Bilayer tablet.

3.2 *In vitro* dissolution study for different formulations.

3.3 Stability study for selected formulation.

3.4 Differential Scanning Calorimetry (DSC) studies.

## 5. Materials and Instruments

### Table: 5.1 Materials and methods

| Sl. No | Materials | Manufacturers/ suppliers |
|---|---|---|
| 1 | Metoprolol Succinate | Aarthi Drugs Ltd, Mumbai. |
| 2 | Hydrochlorothiazide | Benzochem Life Science, Mumbai |
| 3 | Hydroxy propyl methyl cellulose. (HPMC K100M) | Dow Chemicals, Canada |
| 4 | Hydroxypropylmethylcellulose. (HPMC K4M) | Dow Chemicals, Canada. |
| 5 | Lactose DCL 11 | DMV Holland |
| 6 | Maize starch | Vijaya Enterprises, Mumbai. |
| 7 | Povidone (PVP K-30) | Basf, Germany. |
| 8 | Carbomer 971P | Corel Pharma, Gujarat. |
| 9 | Ethyl cellulose 20cps | Basf, Germany. |
| 10 | Microcrystalline cellulose IP (Avicel pH102) | RanQ Remedies, Mumbai. |
| 11 | Microcrystalline cellulose IP (Avicel pH101) | RanQ Remedies, Mumbai. |
| 12 | Colloidal silicon dioxide (Aerosil) | Cobot Sanmar, USA. |
| 13 | Talc | Aravelli pvt. Ltd., New Delhi. |
| 14 | Magnesium stearate | Amshi Drug and Chemicals, Gujarat. |
| 15 | Colour:Brilliant blue lake | Roha Dye Chem, Mumbai. |

## Table: 5.2 Manufacturing Equipments

| Sl. No | Equipments | Manufacturers/ Suppliers |
|---|---|---|
| 1 | Moisture balance | Sartorius, Germany |
| 2 | Vibratory sifter | Bectochem, Mumbai. |
| 3 | Planetary Mixer (vertical main drive) | Bectochem, Mumbai. |
| 4 | Hexagonal blender | Bectochem, Mumbai. |
| 5 | Rapid mixer Granulator | Bectochem, Mumbai. |
| 6 | Fluidized bed dryer | Bectochem, Mumbai. |
| 7 | Tray drier | Micro, S.B.Panchal and Co, India |
| 8 | Multi Mill | Bectochem, Mumbai. |
| 9 | Double Rotary Compression Machine (27 station) | Cadmach, India. |
| 10 | Dehumidifier | Tropical nortec, India |
| 11 | Vernier caliper | Mitutoyo corps, Japan |
| 12 | Blister Packing machine | Lab module, India |
| 13 | Photostability and humidity chamber | Thermolabs India Ltd. |

## Table: 5.3 List of Instruments:

| Sl. No | Instruments | Manufacturers/ Suppliers |
|---|---|---|
| 1 | Electronic weighing balance | Shimadzu corporation, Japan |
| 2 | pH Meter | Mettler, Toledo, India. |
| 3 | Tap Density apparatus, ETD-1020 | Electro lab, India. |
| 4 | Hardness tester | Monsanto , India |
| 5 | Friability Test Apparatus, ET-2 | Electro lab, India. |
| 6 | Dissolution Apparatus, TDT-08L, | Electro lab, India. |
| 7 | FT-IR Spectrophotometer 8300 | Shimadzu corporation, Japan |
| 8 | Differential scanning colorimetry | DSC Q2000 V24.4 build 114 |
| 9 | UV- Visible Spectrophotometer (UV-1601) | Shimadzu corporation, Japan |
| 10 | HPLC with PDA detector | Waters HPLC, India. |
| 11 | Refrigerator | Whirlpool, India |

## Table: 5.4 List of Reagents

| Sl. No | Reagents/ chemicals | Manufacturers/suppliers |
|---|---|---|
| 1 | Potassium dihydrogen ortho phosphate AR | Rankem, New Delhi. |
| 2 | Sodium hydroxide AR | RankemNew Delhi. |
| 3 | Acetonitrile HPLC | Merck Canada. |
| 4 | Methanol HPLC | Merck, Canada. |
| 5 | Sodium dihydrogen ortho phosphate AR | Rankem, New Delhi. |
| 6 | Ortho phosphoric acid AR | Rankem, New Delhi. |
| 7 | Hydrochloric acid AR | Rankem, New Delhi |
| 8 | Whatman filter paper | Sartourious 292A, North America. |
| 9 | 0.45 µ filter paper | Millipore, Canada. |

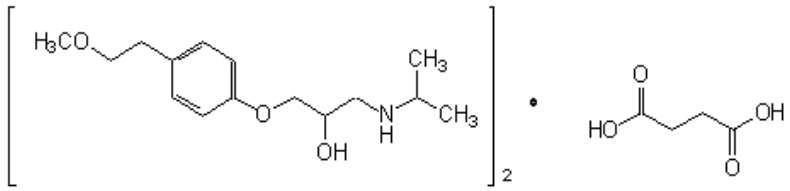
## 5.5 Drug profile

### 5.5.1 Metoprolol succinate USP[71]

**Molecular formula:** $(C_{15}H_{25}NO_3)_2,C_4H_6O_4$

**Molecular weight:** 652.8

**Molecular structure:**




**Chemical Name:**

Description: A white to off-white powder

**Solubility:**

Freely soluble in water; soluble in methyl alcohol; sparingly soluble in alcohol; slightly soluble in isopropyl alcohol

**Melting point:** 120°C (240°F)

**Therapeutic category**: Antihypertensive

**General Description:**

Metoprolol Succinate extended-release tablets are a $beta_1$-selective (cardio selective) adrenoceptor blocking agent, for oral administration, available as extended release tablets. Metoprolol Succinate extended-release tablets have been formulated to provide a controlled and predictable release of Metoprolol for once-daily administration

**Mode of action:**

Metoprolol Succinate, is the selectively blocks beta1-adrenergic receptors in the heart and vascular smooth muscle. The effects of Metoprolol Succinate in treating hypertension include a negative chronotropic effect that decreases heart rate at rest and after exercise; a negative inotropic effect that decreases cardiac output; reduction of sympathetic outflow from the CNS; and suppression of renin release from the kidneys.

**Pharmacokinetics:**

Metoprolol is readily and completely absorbed from the gastrointestinal tract but is subject to considerable first-pass metabolism, with a bioavailability of about 50%. Peak plasma concentrations vary widely and occur about 1.5 to 2 hours after a single oral dose. It is moderately lipid-soluble. Metoprolol is widely distributed; it crosses the blood brain barrier and the placenta, and is distributed into breast milk. It is about 12% bound to plasma protein. It is extensively metabolized in the liver, mainly by the cytochrome P450 isoenzyme CYP2D6, and undergoes oxidative deamination, *O*-dealkylation followed by oxidation, and aliphatic hydroxylation. The metabolites are excreted in the urine with only small amounts of unchanged Metoprolol. The rate of metabolism by CYP2D6 is determined by genetic polymorphism; the half-life of Metoprolol in fast hydroxylators is stated to be 3 to 4 hours, whereas in poor hydroxylators it is about 7 hours.

**Metabolism:**

Metoprolol is metabolized by the cytochrome P450 isoenzyme CYP2D6 and therefore exhibits a debrisoquinetype genetic polymorphism.1-3 Poor, intermediate, extensive, and ultra rapid metabolisers of metoprolol have been identified, and studies4-6 have confirmed that plasma-Metoprolol concentrations correlate with metabolize status. However, the clinical relevance of these differences is less clear. A retrospective study found that the proportion of poor metabolisers among patients who had severe adverse effects was higher than expected, but other studies have found no correlation between the incidence of adverse effects and metaboliser status. Controlled studies in patients with

hypertension and in healthy subjects have found that there is little or no relationship between plasma concentrations or metaboliser status and either the incidence of adverse effects or the response to therapy. The subject may be further confused by variations in the phenotype between ethnic groups. Although the incidence of the poor metaboliser phenotype in whites of European origin is reported to be about 9%, a study in 138 Nigerians failed to identify evidence of polymorphic metabolism, and the authors caution against extrapolation of data between different racial groups.

**Uses:**

Metoprolol is a cardio selective beta blocker. It is reported to lack intrinsic sympathomimetic activity and to have little or no membrane-stabilizing activity. It is used in the management of hypertension, angina pectoris, cardiac arrhythmias, myocardial infarction, and heart failure. It is also used in the management of hyperthyroidism and in the prophylactic treatment of migraine.

**Over dosage:**

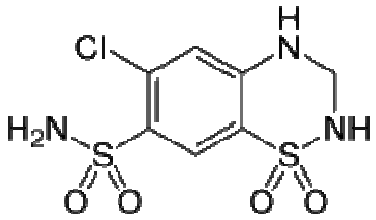
Excessive doses of Metoprolol can cause severe hypotension, bradycardia, metabolic acidosis, seizures and cardio respiratory arrest. Blood or plasma concentrations may be measured to confirm a diagnosis of poisoning in hospitalized patients or to assist in a medico legal death investigation. Plasma levels are usually less than 200 µg/L during therapeutic administration, but can range from 1-20 mg/L in overdose victims.

## 5.5.2 Hydrochlorothiazide IP[74]

**Molecular formula** : $C_7H_8ClN_3O4S_2$

**Molecular weight** : 297.7

**Molecular structure** :




**Chemical Name** : 6-Chloro-3,4-dihydro-2*H*-1,2,4-benzothiadiazine-7-sulphonamide 1,1-dioxide.

**Description** : White to almost white crystalline powder

**Solubility** : A white to almost white coloured crystalline powder.Freely soluble in water, soluble in methanol, sparingly soluble in alcohol and slightly soluble in Isopropyl alcohol

**Melting point** : 274 $^0$C

**Therapeutic category:**

- Antihypertensive Agents
- Diuretics
- Sodium Chloride Symporter Inhibitors

**General Description:**

A thiazide diuretic often considered the prototypical member of this class. It reduces the reabsorption of electrolytes from the renal tubules. This results in increased excretion of water and electrolytes, including sodium, potassium, chloride, and magnesium. It has been used in the treatment of several disorders including edema, hypertension, diabetes insipidus, and hypoparathyroidism.

**Mechanism of Action:**

Thiazide diuretics act in the distal convoluted tubule, where they block Na–Cl co transport. The Na–Cl cotransport takes place on the luminal surface of distal convoluted tubules.Thus, to exert their diuretic action, the thiazides must reach the luminal fluid. Since the thiazide diuretics are largely bound to plasma proteins and therefore are not readily filtered across the glomeruli, access to the luminal fluid is accomplished by the proximal tubule organic acid secretory system. The drugs then travel along the nephron, presumably being concentrated as fluid is abstracted ,until they reach their site of inhibitory action in the distal convoluted tubule. Especially at higher doses, administration of some of the thiazides results in some degree of carbonic anhydrate inhibition. However, at usual doses, only chlorothiazide shows any appreciable carbonic anhydride inhibitory activity.

**Pharmacokinetics**

Hydrochlorothiazide is fairly rapidly absorbed from the gastrointestinal tract. It is reported to have a bioavailability of about 65 to 70%. It has been estimated to have a plasma half-life of between about 5 and 15 hours and appears to be preferentially bound to red blood cells. It is excreted mainly unchanged in the urine. Hydrochlorothiazide crosses the placental barrier and is distributed into breast milk.

**Absorption and Elimination:**

Orally administered thiazides are rapidly absorbed from the gastrointestinal tract and begin to produce dieresis in about 1 hour. Approximately 50% of an oral dose is excreted in the urine within 6 hours. These compounds are organic acids and are actively secreted into the proximal tubular fluid by the organic acid secretary mechanism. There also appears to be an extra renal pathway for their elimination involving the hepatic–biliary acid secretary system that is particularly important for thiazide elimination when renal function is impaired. The thiazides have a variable effect on elimination of uric acid, which also is secreted by the renal acid secretary mechanism. Administration of thiazide diuretics, especially at low doses, may elevate serum uric acid levels and cause

gout like symptoms. Following large doses, thiazides may compete with uric acid for active reabsorption and thereby may promote uric acid elimination rather than impair it.

**Adverse Effects**

Thiazides should be used cautiously in the presence of severe renal and hepatic disease, since azotemia and coma may result. The most important toxic effect associated with this class of diuretics is hypokalemia, which may result in muscular and central nervous system symptoms, as well as cardiac sensitization (see Hypokalemia). Periodic examination of serum electrolytes for possible imbalances is strongly recommended. Appropriate dietary and therapeutic measures for controlling hypokalemia are described later in this chapter. The thiazides also possess some diabetogenic potential, and although pancreatitis during thiazide therapy has been reported in a few cases, the major mechanism contributing to the potential for glucose intolerance is not known.

## 5.6 Excipients profiles:

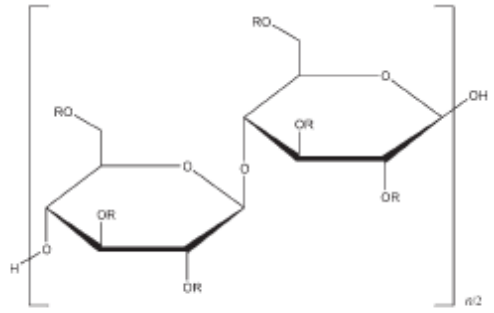
### 5.6.1 Hydroxypropylmethylcellulose[75]

**Nonproprietary Names** : Hypromellose (BP, JP, PhEur, USP)

**Synonym** : Benecel, hydroxypropyl methylcellulose, HPMC, hypromellosum, Methocel, methylcellulose propylene glycol ether, methyl hydroxypropylcellulose, Metolose, pharmacoat.

**Molecular weight** : 10000–1500000.

**Structural Formula**




where R is H, $CH_3$, or $CH_3CH(OH)CH_2$

**Description**

Hypromellose is an odorless and tasteless, white or creamy-white fibrous or granular powder

**Typical Properties**

pH : 5.0–8.0 (2% w/w solution)

Loss on drying : 45.0%

Residue on ignition : 41.5%

Melting point : 190–200$^0$C

**Solubility**

Soluble in cold water, practically insoluble in hot water, chloroform, ethanol (95%), and ether, but soluble in mixtures of ethanol and dichloromethane, mixtures of methanol and dichloromethane and mixtures of water and alcohol.

Nominal viscosity (mPas): 3 - 100000 (2%w/w solution at 20$^{o}$C)

**The different commercial grades are available with varying in viscosities,**

Methocel K4M **:** 4000 mPas

Methocel K15M **:** 15000 mPas

Methocel K100M **:** 100000 mPas

**Functional Category**

Bioadhesive material, coating agent, controlled-release agent, emulsifying agent, extended-release agent, film-forming agent, modified-release agent, solubilizing agent, suspending agent, sustained-release agent, tablet binder, thickening agent.

**Applications in Pharmaceutical Formulation or Technology**

Hypromellose is widely used in oral, ophthalmic, nasal, and topical pharmaceutical formulations. Concentrations between 2% and 5% w/w may be used as a binder in either wet or dry-granulation processes. High-viscosity grades may be used to retard the release of drugs from a matrix at levels of 10–80% w/w in tablets and capsules. Depending upon the viscosity grade, concentrations of 2–20% w/w are used for film-forming solutions to film-coat tablets. Hypromellose at concentrations between 0.45–1.0% w/w may be added as a thickening agent to vehicles for eye drops and artificial tear solutions. It is also used commercially in liquid nasal formulations at a concentration of 0.1%.

**Incompatibilities**

It is incompatible with some oxidizing agents. Since it is nonionic, hypromellose will not complex with metallic salts or ionic organics to form insoluble precipitates.

**5.6.2 Microcrystalline cellulose**

| | | |
|---|---|---|
| **Non proprietary Name** | : | Microcrystalline cellulose, Cellulosummicrocrystallinum. |
| **Empirical formula** | : | $(C_6H_{10}O_5)_n$ Where n = 220 |
| **Molecular weight** | : | 36000 |
| **Applications** | : | It is used primarily as a binder/diluent in oral tablet and capsule formulations where it is used in both wet granulation and direct compression processes. It has also got some lubricant, anti-adherent, and disintegrating properties, which make it useful in tabletting. |

**Typical Properties**

| | | |
|---|---|---|
| Angle of repose | : | 34.4° |
| Density (bulk) | : | 0.337 g/cm$^3$ |
| Density (tapped) | : | 0.478 g/cm$^3$ |
| Flow ability | : | 1.41 g/s |
| Melting point | : | chars at 260 - 270°C. |
| Incompatibilities | : | Incompatible with strong oxidizing agents. |

**Table : Use of Microcrystalline cellulose**

| Use | Concentration (%) |
|---|---|
| Adsorbent | 20-90 |
| Anti adherent | 5-20 |
| Capsule binder/diluents | 20-90 |
| Tablet disintegrant | 5-15 |
| Tablet binder/diluents | 20-90 |

**5.6.3 Colloidal silicon dioxide**

**Nonproprietary Names** : Colloidal anhydrous silica.

**Synonyms** : Aerosil; Cab-O-Sil; Colloidal silica.

**Molecular Weight** : 60.08

**Functional Category** : Adsorbent; anti caking agent; glident; suspending agent; tablet disintegrant; viscosity increasing agent.

**Description** : It is submicroscopic fumed silica with a particle size of about 15 nm it is a light loose bluish white coloured odorless non-gritty amorphous powder

**Bulk density** : 0.029 – 0.042 g/cm³

F**low ability** : 35.52%

**Solubility** : Practically insoluble in organic solvents, water, and acids except hydrofluoric acid soluble in hot solutions of alkali hydroxide. Forms a colloidal dispersion with water.

**Incompatibilities** : Incompatible with diethylstilbestrol.

**Applications:**

It is widely used in pharmaceuticals, cosmetics, and food products also used to stabilize emulsions and as a thixotropic thickening and suspending agent .In aerosols other than those for inhalation colloidal silicon dioxide is used to promote particulate suspension, eliminate hard settling and minimize the clogging of spray nozzles also used as a tablet disintegrant as an adsorbent dispersing agent for liquids in powders or suppositories.

**5.6.4 Povidone**

| | | |
|---|---|---|
| **Nonproprietary Names** | : | Povidone (BP, JP, PhEur, USP) |
| **Synonyms** | : | Kollidon, polyvinylpyrollidone, povidonum, PVP. 1-vinyl-2-pyrollidinone polymer. |
| **Empirical Formula** | : | $(C_6H_9NO)_n$ |
| **Molecular Weight** | : | 2500–3000000 |
| **Description** | : | Povidone occurs as a fine, white to creamy-white colored, odorless or almost odorless, hygroscopic powder. |
| **Solubility** | : | Freely soluble in acids, chloroform, ethanol (95%), ketones, methanol, and water; practically insoluble in ether, hydrocarbons, and mineral oil. |
| **Functional Category** | : | Disintegrant; dissolution enhancer, suspending agent, tablet binder. |

**Applications in Pharmaceutical Formulation or Technology**

In tableting, povidone solutions are used as binders in wet-granulation processes. Povidone is used as a solubilizer in oral and parenteral formulations, and has been shown to enhance dissolution of poorly soluble drugs from solid-dosage forms. Povidone solutions may also be used as coating agents or as binders. Povidone is additionally used as a suspending, stabilizing, or viscosity-increasing agent in a number of topical and oralsuspensions and solutions. The solubility of a number of poorly soluble active drugs may be increased by mixing with povidone.

**Incompatibilities :** It forms molecular adducts in solution with sulfathiazole,sodiumsalicylate, salicylic acid, phenobarbital, tannin, and other compounds.

**5.6.5 Magnesium stearate**

| | | |
|---|---|---|
| **Description** | : | It is a fine, white, precipitated or milled, impalpable powder of low bulk density, having a faint odor of stearic acid and a characteristic taste. The powder is greasy to touch and readily adheres to the skin. |
| **Molecular weight** | : | 591.34 |
| **Structural Formula** | : | $[CH3\ (CH_2)_{16}COO]_2Mg$ |
| **Crystalline Forms** | : | High purity magnesium stearate has been isolated as a trihydrate, a dihydrate, and an anhydrate. |
| **Flow ability** | : | Poorly flowing, cohesive powder. |
| **Melting range** | : | 117-150 $^{o}$C (commercial samples) 126-130 $^{o}$C (high purity magnesium stearate) |
| **Solubility** | : | Practically insoluble in ethanol, |

ether and water; slightly soluble in warm benzene and warm ethanol (95 %)

**Functional category** : Tablet and capsule, lubricant.

**Applications** : It is primarily used as a lubricant in capsule and tablet manufacture at concentrations between 0.25% and 5.0 % w/w.

**Incompatibilities** : Incompatible with strong acids, alkalis, and iron salts. Strong oxidizing materials. Magnesium stearate cannot be used in products containing aspirin, some vitamins and most alkaloidal salts.

**Safety** : Oral consumption of large quantities may result in some laxative effect or mucosal irritation.

**5.6.6 LACTOSE**

**Nonproprietary names** : Lactose (BP), Lactose Monohydrate (PhEUR, USP-NF).

**Synonym** : CapsuLac, GranuLac, Lactochem, lactosum monohydricum, monohydrate, Pharmatose, PrismaLac, SacheLac, SorboLac, pheroLac, SuperTab 30GR, Tablettose.

**Chemical Name** : O-b-D-Galactopyranosyl-(1!4)-a-D-glucopyranose monohydrate,

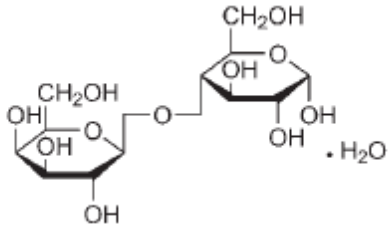
**Emprical Formula** : $C_{12}H_{22}O_{11}\cdot H2O$.

**Molecular weight** : 360.31

**Description:**

In solid state, lactose appears as various isomeric forms, depending on the crystallization and drying conditions, i.e. αlactose monohydrate, β-lactose anhydrous and α-lactose anhydrous. Lactose occurs as white to off-white crystalline particles or powder, it is odorless and slightly sweet-tasting.

**Structural formula:**




**pH** : 5.5-8.9.(1%w/w aqueous solution at $25^{o}$)

**Solubility** : Insoluble in chloroform, ethanol, ether. Soluble in water in

. Ratio of 1 in 5.24.

**Melting point** : 201–$202^{0}$C (for dehydrated a-lactose monohydrate)

**Moisture content** : Lactose monohydrate contains normally

Has a range of 4.5–5.5% w/w water content.

**Functional Category:**

Dry powder inhaler carrier, lyophilization aid, tablet binder, tablet and capsule diluent, tablet and capsule filler.

**Applications in Pharmaceutical formulation or technology:**

Lactose is widely used as a filler and diluent in tablets and capsules. Lactose is also used as a diluent in dry-powder inhalation. Lactose is added to freeze-dried solutions to increase plug size and aid cohesion. Lactose is also used in combination with sucrose to prepare sugar-coating solutions. It may also be used in intravenous injections. Lactose

is also used in the manufacture of dry powder formulations for use as aqueous film-coating solutions or suspensions. Direct-compression grades of lactose monohydrate are available as spray-dried lactose and anhydrous lactose.

**Incompatibilities:**

A Maillard-type condensation reaction is likely to occur between lactose and compounds with a primary amine group to form brown, or yellow-brown-colored products. Lactose is also incompatible with amino acids, amfetamines and lisinopril.

**Stability and storage conditions:**

Mold growth may occur under humid conditions (80% relative humidity and above). Lactose may develop a brown coloration on storage, the reaction being accelerated by warm, damp conditions. Solutions show autorotation. Lactose should be stored in a well-closed container in a cool, dry place.

**Safety:**

Lactose is widely used as a filler and filler-binder in orals and injections. Adverse reactions to lactose are largely attributed to lactose intolerance, results in lactose being undigested and may lead to cramps, diarrhea, distension, and flatulence.

**5.6.7 STARCH:**

**Nonproprietary Names**

Maize starch, Potato starch, Rice Starch, Tapioca Starch, Wheat Starch (BP, JP, PhEur, USP)

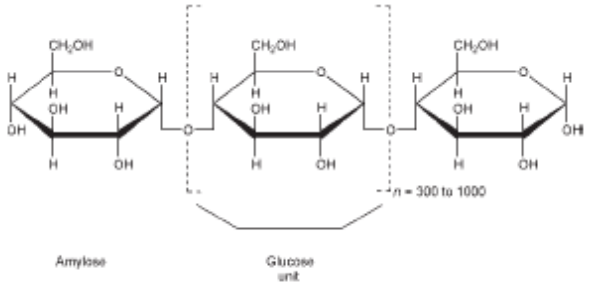
**Synonyms**

Amido, amidon, amilo, amylum, C*PharmGel, Eurylon, fecule, Hylon, maydis amylum, Melojel, Meritena, oryzae amylum, Pearl, Perfectamyl, pisi amylum, Pure-Dent, Purity 21, Purity 826, solani amylum, tritici amylum, Uni-Pure.

**Empirical Formula** : $(C_6H_{10}O_5)_n$ where n = 300–1000.

**Molecular Weight** : 50 - 500 million Da

**Structural Formula**




**Description**

Starch occurs as an odorless and tasteless, fine, white to off-white powder. It consists of very small spherical or ovoid granules or grains whose size and shape are characteristic for each botanical variety.

**Typical Properties**

pH : 4.0–8.0

**Moisture content**

All starches are hygroscopic and absorb atmospheric moisture to reach the equilibrium humidity. The approximate equilibrium moisture is 12 – 18 %

**Solubility**

Practically insoluble in cold ethanol (96%) and in cold water. Starch becomes soluble in hot water at temperatures above the gelatinization temperature. Starches are partially soluble in dimethylsulfoxide and dimethylformamide.

**Functional Category**

Tablet and capsule diluent; tablet and capsule disintegrate; tablet binder; thickening agent.

**Applications in Pharmaceutical Formulation or Technology**

Starch act as an antiadherent and lubricant in tableting and capsule filling (3–10% w/w).In tablet formulations, freshly prepared starch paste is used at a concentration of 3–20% w/w (usually 5–10%, depending on the starch type) as a binder for wet granulation. Starch is one of the most commonly used tablet disintegrants at concentrations of 3–25% w/w;a typical concentration is 15%.Starch, particularly the fine powders of rice and wheat starch, is also used in topical preparations for its absorbency of liquids.Starch paste is used in ointment formulations, usually in the presence of higher ratios of glycerin.Starch has been investigated as an excipient in novel drug delivery systems for nasal, and other site-specific delivery systems (colon). They can improve the bioavailability of poorly soluble drugs.Starch has also been used in the treatment of children's diarrheal diseases.Starches with a high amylopectin content (waxy starches) are used as the starting material for the synthesis of hydroxyethyl starch, a plasma volume expander.

**Stability and Storage Conditions**

Dry starch is stable if protected from high humidity.Starch should be stored in an airtight container in a cool, dry place

.**Incompatibilities**

Starch is incompatible with strongly oxidizing substances. Colored inclusion compounds are formed with iodine.

**Safety:**

It is regarded as an essentially nontoxic and nonirritant material. Both amylose and amylopectin have been evaluated as safe and without limitation for daily intake.

### 5.6.8 ISOPROPYL ALCOHOL

**Nonproprietary Names**

Isopropyl Alcohol (BP, JP, PhEur, USP)

**Synonyms**

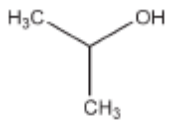
Alcohol isopropylicus, dimethyl carbinol, IPA, isopropanol, petrohol, 2-propanol, sec-propyl

**Chemical Name** : Propan-2-ol

**Empirical Formula** : $C_3H_8O$

**Molecular Weight** : 60.1

**Structural Formula**




**Description**

Isopropyl alcohol is a clear, colorless, mobile, volatile, flammable liquid with a characteristic, spirituous odor and it has a slightly bitter taste.

**Typical Properties**

Boiling point : $82.4^0$C

Flammability : Flammable.

Viscosity (dynamic) : 2.43 mPas at $20^0$C

Specific gravity : 0.786

**Solubility**

Miscible with benzene, chloroform, ethanol (95%), ether, glycerin, and water. Soluble in acetone; insoluble in salt solutions.

**Functional Category:** Disinfectant, solvent.

**Applications in Pharmaceutical Formulation or Technology**

Isopropyl alcohol is also used as a solvent both for tablet film-coating and for tablet granulation, where the isopropyl alcohol is subsequently removed by evaporation. It has also been shown to significantly increase the skin permeability of nimesulide. Isopropyl alcohol has some antimicrobial activity and a 70% v/v aqueous solution is used as a topical disinfectant. Therapeutically, isopropyl alcohol has been investigated for the treatment of postoperative nausea or vomiting.

**Storage Conditions**

Isopropyl alcohol should be stored in an airtight container in a cool, dry place.

**Incompatibilities**

Incompatible with oxidizing agents such as hydrogen peroxide and nitric acid, which cause decomposition.

**Safety:**

Isopropyl alcohol is most frequently used in topical pharmaceutical formulations where it may act as a local irritant. When applied to the eye it can cause corneal burns and eye damage.

## 6. Experimental work

### 6.1 Preformulation studies

#### 6.1.1 Raw material analysis of Metoprolol Succinate USP[70]:

Raw material analysis of Metoprolol Succinate was done as per USP by the identification test carried out by the Fourier Transform Infra red spectrophotometer (FTIR) and the report was shown in fig: 1

#### 6.1.2 Raw material analysis of Hydrochlorothiazide IP[72]:

Raw material analysis of Hydrochlorothiazide was done as per IP by the identification test carried out by the Fourier Transform Infra red spectrophotometer (FTIR) and the reports were shown in fig: 2

#### 6.1.3 Drug-Excipients compatibility studies:

In the tablet dosage form the drug is in intimate contact with one or more excipients; the latter could affect the stability of the drug. Knowledge of drug-excipient interactions is therefore very useful to the formulator in selecting appropriate excipients. This information may be present for known drugs. For new drugs or new excipients, the preformulation scientist must generate the needed information.

#### 6.1.4 Physical observation:

Active ingredients were mixed well with all excipients in binary ratio and small portion of this mixed powder was placed in cleaned and dried vial in stability chamber at $40^{o}C \pm 2^{o}C$ / $75 \pm 5\%$ RH and $25^{o}C \pm 2^{o}C$ /$60 \pm 5\%$ RH. Physical observation has been carried out visually for 14days and 28days.

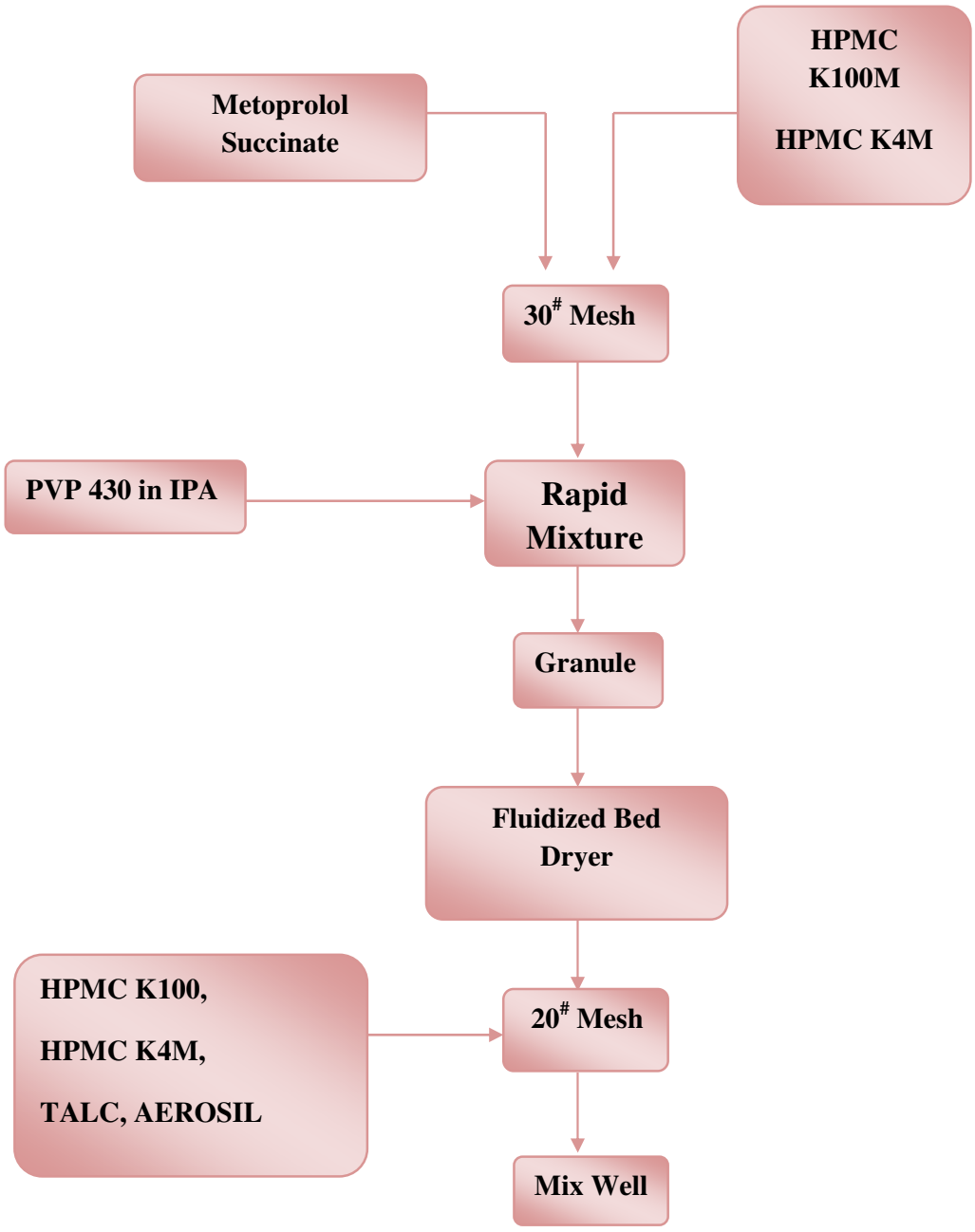
**6.2 Manufacturing process of Bilayer tablets**:

Based on the inferences from excipient compatibility studies, the compatible excipient were used for formulation and development using suitable processes. Development trials of about 5000 tablets were made and evaluated the physical parameters of the blend and the compressed tablets. Such development trial taken until tentative formula.

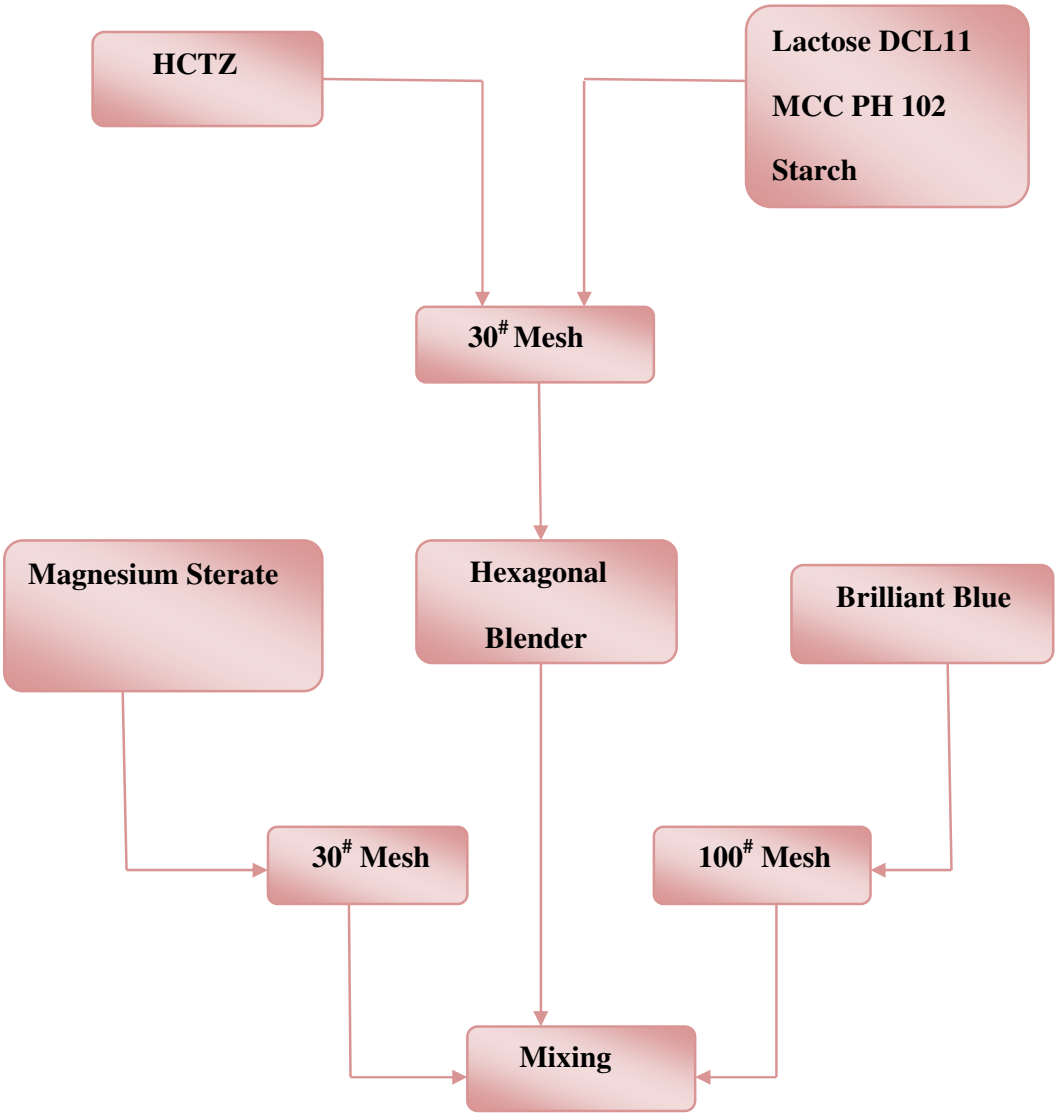
**6.2.1 Manufacturing process of Metoprolol Succinate sustained release granules*:***

Weighed quantity of Metoprolol Succinate, Microcrystalline cellulose PH102, Hydroxy propyl methyl cellulose K100M and Hydroxy propyl methyl cellulose K4M were sifted through #30 mesh sieve and mixed for 10 minutes in rapid mixer granulator. The binder solution containing poly vinyl pyrollidone K30 in Isopropyl alcohol was added slowly to the above ingredients and mixed at slow speed, after complete addition of binder solution mix well to get the granules. The wet granules were loaded in a fluidized bed drier and dried till the moisture content of granules are between 2.0 to 3.0. The dried granules were sifted through #20 mesh sieve, Hydroxy propyl methyl cellulose K100, Hydroxy propyl methyl cellulose K4M, Colloidal silicon dioxide and purified talc were loaded in planetary mixer along with the dried granules and mixed well for 3 minutes at slow speed.

**Flow chart of Metoprolol Succinate Granules preparation**



**Flow Chart of Hydrochlorothiazide Granules preparation**



### 6.2.2 Manufacturing process of Hydrochlorothiazide Immediate Release granules:

Weighed quantity of Hydrochlorothiazide, Microcrystalline cellulose PH102, Lactose DCL 11 and Maize starch were sifted through #30 mesh sieve and mixed for 10 minutes in Hexagonal blender. Colloidal silicon dioxide and magnesium Sterate sift through #30 mesh and Brilliant blue lake sift through #100 mesh were loaded in blender along with the above sifted material and mixed well for 2 minutes at slow speed.

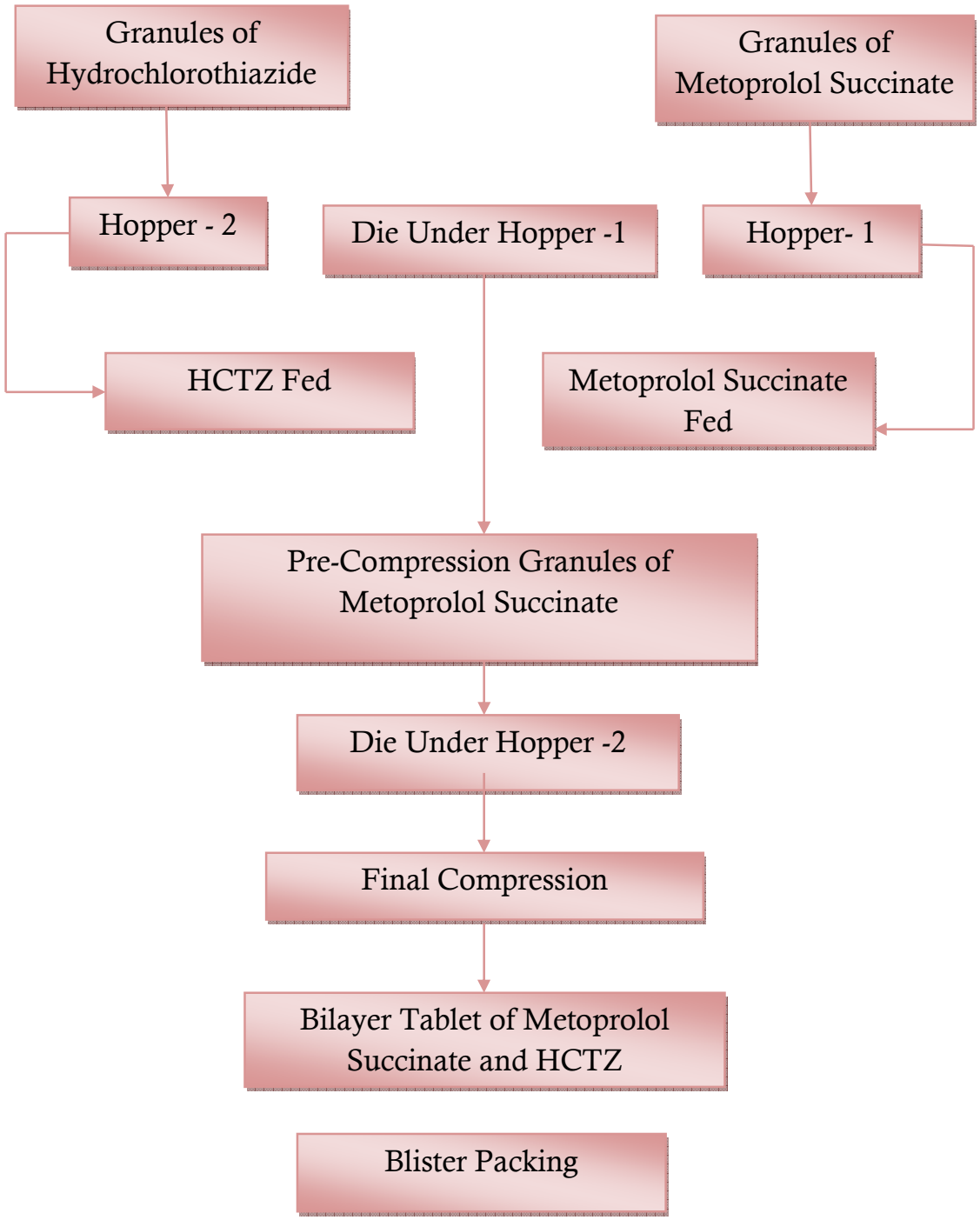
### 6.2.3 Compression of Bilayer tablets:

The quantity of granules for the immediate-release layer was compressed lightly using 27 stationary double rotary compression machine (Cad mach, India) using 14/32 inch circular shaped plain punches. Over this compressed layer, required quantity of the sustained release layer was placed and compressed to obtain hardness in the range of 8-12 kg/cm² to form a bilayer tablet of sustained release of Metoprolol succinate and immediate release of Hydrochlorothiazide. Then the compressed bilayer tablets were evaluated.

### 6.2.4 Packing of Bilayer tablets (Blister packing):

The compressed bilayer tablets were blister packed using Aluminum foil (0.025mm thickness) and PVC foil (0.25mm thickness) with blister packing machine (PGI pack 240CH). This blister was evaluated for leakage by dipping two blister in water and apply vacuum for 2 minutes, then check it.

**Flow Chart of Bilayer Tablets Of Metoprolol Succinate and Hydrochlorothiazide Preparation**



## 6.5 Evaluation

### 6.5.1 Evaluation of granules: [76]

**Bulk density:**

Bulk density is the ratio of the weight of the powder to the bulk volume it occupies. it is expressed in gm/ml. Weighed quantity of granules was transferred into a 50 ml measuring cylinder without tapping, during transfer the volume occupied by granules was measured. Bulk density was measured by using formula.

$$\mathbf{P = m/V_o}$$

Where,

$P_i$ = Bulk density

m = Mass of the blend,

$V_o$ = Untapped Volume

**Tapped Density:**

Weighed quantity of granules was taken into graduated cylinder, volume occupied by granules was noted down. Then cylinder was subjected to 500 taps in tapped density tester (Electro Lab USP II), the % Volume variation was calculated by following formula.

$$\mathbf{P_t = m/V_i}$$

Where,

$P_t$ = Tapped density

M = Mass of the blend,

$V_i$ = Tapped volume

**Carr's compressibility index:**

Compressibility is the ability of powder to decrease in volume under pressure. Using untapped density and tapped density the percentage compressibility of granules were determined, which is given as Carr's compressibility index.

$$CI = V_i - V_0 / V_i \times 100$$

Where,

CI = Compressibility index

Vo = Bulk density

$V_i$ = Tapped density

**Table: Compressibility index**

| Compressibility index (%) | Flow characters |
|---|---|
| < 10 | Excellent |
| 11-15 | Good |
| 16-20 | Fair |
| 21-25 | Passable |
| 26-31 | Poor |
| > 32 | Very poor |

**Hausner Ratio**

It is measurement of frictional resistance of the drug. It was determined by the ratio of tapped density and bulk density.

$$\text{Hausner Ratio} = Vo/V_i$$

Where,

Vo = Bulk density

$V_i$ = Tapped density

**Table: Hausner ratio**

| Flow characters | Hausner ratio |
|---|---|
| Excellent | 1.11 |
| Good | 1.12 – 1.18 |
| Fair | 1.19 – 1.25 |
| Passable | 1.26 – 1.34 |
| Poor | 1.35 – 1.45 |
| Very poor | 1.46 – 1.59 |
| Very Very poor | >1.60 |

**Angle of repose:**

Angle of Repose (θ) is the maximum angle between the surface of a pile of powder and horizontal plane. It is usually determined by fixed funnel method and is the measure the flow ability of powder/granules.

**Procedure:**

Weighed quantity of granules was passed through a funnel kept at a height of 2 cm for the base. The powder is passed till it forms heap and touches the tip of the funnel. The radius was measured and angle of repose was calculated by using the formula.

$$\theta = \tan^{-1}(h/r)$$

Where,

θ = Angle of repose

h = height of the heap of pile,

r = radius of base of pile

**Table: Flow Properties and Corresponding Angle of Repose**

| Flow properties | Angle of repose (θ) |
|---|---|
| Excellent | 25-30 |
| Good | 31-35 |
| Fair – aid | 36-40 |
| Passable | 41-45 |
| Poor | 46-55 |
| Very poor | 56-65 |
| Very Very poor | >66 |

**Moisture content:**

Initially 5 g of weighed granules were taken and kept for drying at $105^0$ C for a required time in a oven. Then removed and again reweighed and noted as final weight. The difference in weight was noted as moisture content.

$$\text{Moisture content} = \frac{\text{initial weight – final weight}}{\text{Initial weight}} \times 100$$

**Evaluation of Metoprolol granules:**

Metoprolol granules were evaluated for its bulk density, tapped density, Carr's index, Hausner ratio, angle of repose and moisture content as per the procedure followed for Metoprolol granules. Their results are tabulated in table no.7.6, 7.7.

### 6.5.2 Evaluation of tablets [77]

#### 6.5.2.1 Evaluation of physical characteristics

The formulated tablets were evaluated for the following physicochemical parameters,

**Thickness:**

Thickness mainly depends on die filling, physical properties of material to be compressed under compression force. There is bound to be a small variation in the thickness of individual tablet in a batch. But it should not be apparent to the unaided eye. The thickness and diameter were measured by using vernier calipers.

**Hardness:**

Tablet requires certain amount of strength or hardness, measured by Monsanto hardness tester. Ten tablets were randomly picked from each formulation and evaluated for hardness during manufacturing and is expressed in $Kg/cm^{2.}$ .

**Friability:**

Friability was performed by using Roche friabilator, normally pre weighed ten tablets were placed in the plastic chamber of friabilator. This was then operated for 100 revolutions. Tablets dropping from a distance of six inches with each revolution. Tablets are then dusted and reweighed. Loss of less than 1% in weight is considered to be acceptable.

$$F\ (\%) \quad \frac{\text{Initial wt.} - \text{Final wt.}}{\text{Initial wt.}} \times 100$$

**Weight variation test:**

Twenty tablets were selected randomly and weighed individually. Calculate average weight and compare the individual tablet weight to the average. Not more than two of the individual weights deviate from the average weight by more than the percentage shown in table and none deviate by more than twice the percentage.

**6.5.2.2: Assay:**

**Assay for Metoprolol Succinate and Hydrochlorothiazide [50]:**

Chromatographic system:

| | |
|---|---|
| Apparatus | : HPLC, PDA detector |
| Column | : Inertsil ODS C18,250× 4.6 mm, 5µ |
| Flow rate | : 1.0 ml/min |
| Wave length | : 222 nm |
| Injection volume | : 20µl |
| Column temperature | : Ambient |

Diluent:

1st diluents –Methanol and 2nd diluents – Mobile phase.

Mobile phase :

Mix 85 parts of Buffer and 15 parts of Acetonitrile

**Preparation of standard solution:**

Accurately weighed 23.5mg of Metoprolol succinate and 12.4mg Hydrochlorothiazide was taken in 100ml volumetric flask and to this 50ml of methanol was added and sonicated to dissolve and volume was made up with methanol. From this 5ml of above solution was pipetted out in to 50 ml volumetric flask and volume was made up with mobile phase.

**Preparation of sample solution:**

One tablet equivalent to 52.5mg of Metoprolol succinate was taken in 100ml volumetric flask and 70ml of methanol was added and sonicated for 30min and volume was made up with methanol. From this 10ml of above solution was pipetted out in to 50ml volumetric flask and volume was made up with mobile phase.

**System suitability:**

% RSD of five replicate injections peak should not be more than 2.0%

The theoretical plate for Metoprolol Succinate and Hydrochlorothiazide peaks should not less than 1500. The tailing factor Metoprolol Succinate and Hydrochlorothiazide peaks should not more than 2.0

**Procedure:**

20 micro liters of filtered portion of the standard solution and sample solution was injected in to HPLC system. The chromatogram was recorded and responses were measured for the major peaks. The content of Metoprolol succinate and Hydrochlorothiazide per tablet was calculated and followed by the expression.

**Calculation:**

**For Metoprolol tartrate**

$$= \frac{\text{Spl Area}}{\text{Std Area}} \times \frac{\text{Std. wt}}{100} \times \frac{5}{50} \times \frac{100}{LC} \times \mathbf{X} \frac{50}{5} \times \frac{\text{Purity}}{100} \times \frac{\text{Avg wt}}{LC} \times \frac{684.81^*}{652.81^{**}} \times 100$$

*- Molecular weight of Metoprolol tart rate
** - Molecular weight of Metoprolol Succinate

**For Hydrochlorothiazide**

$$= \frac{\text{Spl Area}}{\text{Std Area}} \times \frac{\text{Std. wt}}{100} \times \frac{5}{50} \times \frac{100}{LC} \times \mathbf{X} \frac{50}{5} \times \frac{\text{Purity (as is)}}{100} \times \frac{\text{Avg wt}}{LC} \times 100$$

***In vitro* Dissolution studies:**

**Dissolution for Metoprolol Succinate[30, 70]:**

Six tablets of Metoprolol and Hydrochlorothiazide (Bilayer tablets) were placed in the apparatus of USP II (paddle). The medium used was 500 ml of pH 6.8 phosphate buffer solutions and the dissolution mediums were maintained at the temperature of 37.5± $0.5^0$ C the RPM was fixed in 50 RPM. The sample was

withdrawn at of 1st, 4th, 8th and 20th hr time interval. The estimation was carried out by HPLC method

**Chromatographic system:**

Apparatus : HPLC, PDA Detector

Column : Inertsil ODS C18, 250× 4.6 mm,5µ

Wave length : 222 nm

Injection volume : 20 µl

Flow rate : 1.0 ml/min

Column Temperature : Ambient

Diluent : Dissolution medium

Mobile phase : Mix 85 parts of Buffer and 15 parts of Acetonitrile

**Standard preparation:**

Accurately weighed 23.5mg of Metoprolol succinate was taken in 50ml of volumetric flask and 25ml of diluents were added and sonicated to dissolve and the volume was made up with diluents. From this 5ml was pipetted out in to 50ml volumetric flask and volume was made with a diluents. Filtered through 0.45 micron membrane filter.

**Sample preparation:**

The dissolution parameters were setted and one tablet is placed in each basket and care was taken to exclude air bubbles from the surface of the tablets and immediately the apparatus was started after 1st hour, 10ml of the sample was withdrawn and filter through whatmann filter paper, 10ml of solution was replaced in to dissolution medium, the same procedure was repeated at 4th, 8th and 20th hour.

**Procedure:**

20 micro liters of filtered portion of the standard and sample solution was injected in to HPLC system. The chromatogram was recorded and responses were

measured for major peaks. The % release of Metoprolol succinate was calculated by using following expression.

**Calculation for Metoprolol Succinate:**

$$= \frac{\text{Spl Area}}{\text{Std Area}} \times \frac{\text{Std. wt}}{50} \times \frac{5}{50} \times \frac{500}{LC} \times \textbf{X} \frac{\text{Purity (as is)}}{100} \times \frac{684.81^*}{652.81^{**}} \times 100$$

*- Molecular weight of Metoprolol tartrate
** - Molecular weight of Metoprolol Succinate

**Dissolution for Hydrochlorothiazide:**

Six tablets of Metoprolol and Hydrochlorothiazide (bilayer tablets) were placed in the apparatus of USP I (Basket). The medium used was the 900 ml of 0.1N Hydrochloric acid solutions and the dissolution mediums maintained at the temperature of 37.5± $0.5^0$ C the RPM was fixed in 100 RPM. The sample withdrawal time of 1hr (60 min). The estimation was carried out by HPLC method.

**Chromatographic system:**

| | |
|---|---|
| Apparatus | : HPLC, PDA Detector |
| Column | : Inertsil ODS C18, 250× 4.6 mm, 5µ |
| Wave length | : 222 nm |
| Injection volume | : 100 µl |
| Flow rate | : 1.0 ml/min |
| Column Temperature | : Ambient |
| Diluents | : Dissolution medium |
| Mobile phase | : Mix 85 parts of Buffer and 15 parts of Acetonitrile |

**Standard preparation:**

Accurately weighed 12.4mg of Hydrochlorothiazide was taken in 200ml volumetric flask and 50ml of diluents, kept warm at 50˚C in water bath for 20mins to dissolve and volume was made up by the diluents. From this 5ml was pipetted out in to 100ml volumetric flask and volume was made up with dissolution medium.

**Sample preparation**

The dissolution parameters were setted and one tablet was placed in to each basket care was taken to exclude air bubbles from the surface of the tablets and immediately the apparatus was started, after $60^{th}$ min the sample was withdrawn by using whatmann filter.

**Procedure**

100 micro liters of filtered portion of the standard and sample solution was injected in to HPLC system. The chromatogram was recorded and the responses were measured for the major peaks. The % release of Hydrochlorothiazide was calculated an calculated and followed by the expression.

**Calculation for Hydrochlorothiazide:**

$$= \frac{\text{Spl Area}}{\text{Std Area}} \times \frac{\text{Std. wt}}{200} \times \frac{5}{50} \times \frac{900}{LC} \times \text{Purity (as is)} \times X100$$

**6.6 Kinetics of drug release** [77]

Kinetics of drug release is studied by plotting the data obtained from *in vitro* release in various kinetic models.

**Zero order equation**

The graph was plotted as % drug released Vs time in hours.

$$C=K_0t$$

Where,

$K_0$ – Zero order constant in concentration/time

t – Time in hours

The graph would yield a straight line with a slope equal to $K_0$ and intercept the origin of the axis. The results were tabulated and graph was shown.

**First order equation**

The graph was plotted as log % cumulative drug remaining Vs Time in hours.

$$\textbf{Log C = log } C_0 \textbf{- Kt /2.303}$$

Where,

$C_0$ - Initial concentration of drug.

K- First order constant.

t- Time in hours

**Higuchi kinetics**

The graph was plotted as % Cumulative drug released Vs square root of time

$$Q = Kt^{1/2}$$

Where,

K – Constant reflecting design variable system.

t - Time in hours

Hence drug release rate is proportional to the reciprocal of square root of time. If the plot yields a straight line, and the slope is one, then the particular dosage form is considered to follow Higuchi kinetics of drug release. The results were tabulated.

**Korsmeyer – Peppas equation**

To evaluate the mechanism of drug release, it was further plotted in peppas equation as log cumulative % of drug released Vs time

$$M_t / M\alpha = Kt^n$$

**Log $M_t$ / M α = log K + n log t**

Where,

$M_t$ / Mα - fraction of drug released at time t

t – Release time `

K – Kinetic constant (incorporating structural and geometric characteristics of preparation)

n - Diffusion exponent indicative of the mechanism drug release.

If n value is 0.5 or less, the release mechanism follows " Fickian diffusion" and higher values of 0.5 < n< 1 for mass transfer follow a non- fickian model (anomalous transport). The drug release follows zero-order drug release and case – II transport if the value is 1. For the values of n higher than 1, the mechanism of drug release is regard as super case II transport. This model is used to analyze the release of pharmaceuticaL polymeric dosage forms when the release mechanism is not known or more than one type of release phenomenon was involved. The n value could be obtained from slope of the plot of log cumulative % of drug released Vs log time.

**6.7 Stability studies:** [69, 78]

Stability of a drug has been defined as the ability of a particular formulation, in a specific container, to remain within its physical, chemical, therapeutics and toxicological specifications. The purpose of stability testing is to provide evidence on how the quality of a drug substance or drug product varies with time under the influence of a variety of environmental factors such as temperature, humidity and light, and to establish a retest for the drug substance or a shelf life for the drug product and recommended storage conditions. The selected batches were charged on accelerated stability as per ICH guidelines.

**Table: Storage condition**

| S.NO. | STUDY | STORAGE CONDITION |
|---|---|---|
| 1 | Long term | 25°C±2°C/60%RH±5%RH |
| 2 | Accelerated | 40°C±2°C/75%RH±5%RH |

**Stability studies of selected formulations:**

Stability studies were conducted for the formulation F-8 and F-9 .The storage conditions used for stability studies were accelerated condition (40°C±2°C/75%±5%RH) and ambient temperature (30°C±2°C/65%±5%RH). Sample of tablets were analyzed after 1 month and 2 months for physical characters and assay were performed followed by in vitro dissolution test.

**Test Performed:**

1. Test for physical parameters (description, weight variation, friability).
2. Assay
3. *In vitro* Dissolution Study

### 6.8 FT-IR Studies: [30, 70, 72]

Physical compatibility studies were assured by FT-IR studies. The IR spectrums of the mixed powders were taken by preparing Potassium bromide pellets under dry condition by using pellet press. Superimposed these spectra. The transmission minima (absorption maxima) in the spectra obtained with the sample corresponded in position and relative size to those in the spectrum obtained with the working/reference standards.

### 6.9 Differential Scanning Calorimeter (DSC): [28, 35]

DSC studies also performed to investigate the physical state of the drug in the tablets and to know the interactions of drug with polymers in the formulation. Thermal properties of pure drug and the formulation were evaluated by (DSC) using Q2000 24.4 build 116.

The tablet was ground to powder and a 1-2 mg sample was hermetically sealed in an aluminum pan and heated at a constant rate of 10ºC/min from 30ºC to 300ºC temperature range. Inert atmosphere was maintained by purging nitrogen gas at a flow rate of 20 ml/min.

**Table: 7.1 Drug – Excipient compatibility study**

**Physical Observation**

| Sl. No | Drug+Excipient | Parameter | Initial Value of Parameter | Condition | | | | Comments |
|---|---|---|---|---|---|---|---|---|
| | | | | RT40°C±2°C/75% ±5%RH | | RT25°C±2°C/60% ±5%RH | | |
| | | | | 14 days | 28 days | 14 days | 28 days | |
| 1 | **Metoprolol Succinate** | Any colour change | No colour change | No colour change | No colour change | No colour change | No colour change | Compatible |
| 2 | **Hydrochlorothiazide** | Any colour change | No colour change | No colour change | No colour change | No colour change | No colour change | Compatible |
| 3 | **Metoprolol succinate + Hydrochlorothiazide** | Any colour change | No colour change | No colour change | No colour change | No colour change | No colour change | Compatible |
| 4 | **Metoprolol succinate + Hydrochlorothiazide + excipients** | Any colour change | No colour change | No colour change | No colour change | No colour change | No colour change | Compatible |
| 5 | **Placebo** | Any colour change | No colour change | No colour change | No colour change | No colour change | No colour change | Compatible |

**Table: 7.2 Evaluation of Bilayer tablets of Metoprolol succinate SR and Hydrochlorothiazide IR (F-1 to F-5)**

| Sl. No | Tests | Specifications | F - 1 | F - 2 | F - 3 | F - 4 | F - 5 |
|---|---|---|---|---|---|---|---|
| 1. | Description | Blue / White colored circular shaped uncoated Bilayer tablet | Complies with internal Specifications | Complies with internal Specifications | Complies with internal Specifications | Complies with internal Specifications | Complies with internal Specifications |
| 2. | Average weight (mg) | 375 mg±3% | 376.2 mg | 376.2 mg | 377.2 mg | 377.2 mg | 376.8 mg |
| 3. | Thickness* (mm) | 4.80±0.2 | 4.82±0.2 | 4.82±0.2 | 4.78±0.2 | 4.78±0.2 | 4.80±0.2 |
| 4. | Hardness* (kg/cm2) | NLT 3.0 | 6.5±0.02 | 6.5±0.02 | 6.5±0.3 | 7.0±0.02 | 6.5±0.02 |
| 5. | Friability *(% w/w) | NMT 1% | 0.02±0.01 | 0.02±0.01 | 0.21±0.01 | 0.19±0.01 | 0.21±0.01 |
| 6. | Weight variation (n=20) | ±5% from the average weight | +2.1 to -2.3 | +2.1 to -2.3 | +2.8 to -2.7 | +3.7 to -2.9 | +2.1 to -2.3 |
| 7. | Assay | | | | | | |
| | a) Metoprolol succinate equivalent to Metoprolol tartarate | 90 – 110% | 95.2% | 95.7% | 96.4% | 96.2% | 96.4% |
| | b) Hydrochlorothiazide | 90 – 110% | 96.2% | 96% | 97.1% | 98.2% | 97.1% |

*** All the values are mean ±SD, n=6.**

**Table: 7.3 Evaluation of Bilayer tablets of Metoprolol succinate SR and Hydrochlorothiazide IR (F-6 to F-9)**

| Sl. No | Tests | Specifications | F - 6 | F - 7 | F - 8 | F - 9 |
|---|---|---|---|---|---|---|
| 1. | Description | Blue / White colored circular shaped uncoated Bilayer tablet | Complies with internal Specifications | Complies with internal Specifications | Complies with internal Specifications | Complies with internal Specifications |
| 2. | Average weight (mg) | 375±3% | 377.4mg | 376.2 mg | 375.2 mg | 375.2 mg |
| 3. | Thickness *(mm) | 4.80±0.2 | 4.78±0.2 | 4.78±0.2 | 4.78±0.2 | 4.80±0.2 |
| 4. | Hardness* (kg/cm²) | NLT 3.0 | 6.9±0.02 | 7.0 | 7.0 | 6.8 |
| 5. | Friability* (% w/w) | NMT 1% | 0.34±0.01 | 0.22±0.01 | 0.19±0.01 | 0.19±0.01 |
| 6. | Weight variation (n=20) | ±5% from the average weight | +3.2 to -2.8 | +3.1 to -2.1 | +3.5 to -2.9 | +3.1 to -2.1 |
| 7. | Assay | | 96.6% | | | |
| | a) Metoprolol succinate equivalent to Metoprolol tartarate | 90 – 110% | 97.6% | 96.2% | 99.4% | 99.4% |
| | b) Hydrochlorothiazide | 90 – 110% | | 97.1% | 99.7% | 99.7% |

*** All the values are mean ±SD, n=6.**

**7.4 Dissolution studies**

***In vitro dissolution profile of Bilayer tablet* F-1**

| **Sustained release layer of Metoprolol succinate** | | | | |
|---|---|---|---|---|
| **Sl. No** | **Time (hr)** | **Limit (%)** | **Amount of drug release (mg)** | **Cumulative % drug release*** |
| 1. | 1 | NMT 25% | 11.57 | 46.28±0.03 |
| 2. | 4 | 20 – 40 | -- | -- |
| 3. | 8 | 40 – 60 | -- | -- |
| 4. | 20 | NLT 80% | -- | -- |
| **Immediate release layer of Hydrochlorothiazide** | | | | |
| **Sl. No** | **Time (hr)** | **Limit (%)** | **Amount of drug release (mg)** | **Cumulative % drug release*** |
| 1. | 1.0 | NLT 60% | -- | -- |

***all the values are mean ±RSD, n=6**

In the above table gives the *in vitro* dissolution profile of Metoprolol succinate sustained release and Hydrochlorothiazide immediate release tablet for the formulation F-1. The drug release of Metoprolol succinate at 1st hour was found to be 46.28% which is above in the limit , so that dissolution was stopped.

The release of Hydrochlorothiazide was not found as the tablet compressibility is less.

In below Fig: 1 shows the graph of *in vitro* drug release profile of sustained release of Metoprolol succinate and immediate release of Hydrochlorothiazide for formulation F-1

***In vitro dissolution profile of Bilayer tablet* F-2**

| **Sustained release layer of Metoprolol succinate** | | | | |
|---|---|---|---|---|
| **Sl. No** | **Time (hr)** | **Limit (%)** | **Amount of drug release (mg)** | **Cumulative % drug release*** |
| 1. | 1 | NMT 25% | 3.58 | 14.33±0.04 |
| 2. | 4 | 20 – 40 | 17.46 | 69.84±0.05 |
| 3. | 8 | 40 – 60 | -- | --- |
| 4. | 20 | NLT 80% | -- | --- |
| **Immediate release layer of Hydrochlorothiazide** | | | | |
| **Sl. No** | **Time (hr)** | **Limit (%)** | **Amount of drug release (mg)** | **Cumulative % drug release*** |
| 1. | 1.0 | NLT 60% | 10.29 | 82.33±0.04 |

***all the values are mean ±RSD, n=6**

In the above table gives the *in vitro* dissolution profile of Metoprolol succinate and Hydrochlorothiazide immediate release tablet for the formulation F-2. The drug release of metoprolol succinate at 1st, 4th hour was found to be 14.33, 69.84 respectively. The 4th hour release is above in the limit.

The release of Hydrochlorothiazide at the end of 1 hour was found to be 82.33%.

In the below Fig: 2 shows the graph of *in vitro* drug release profile of sustained release of Metoprolol succinate and immediate release of Hydrochlorothiazide for the formulation F-2

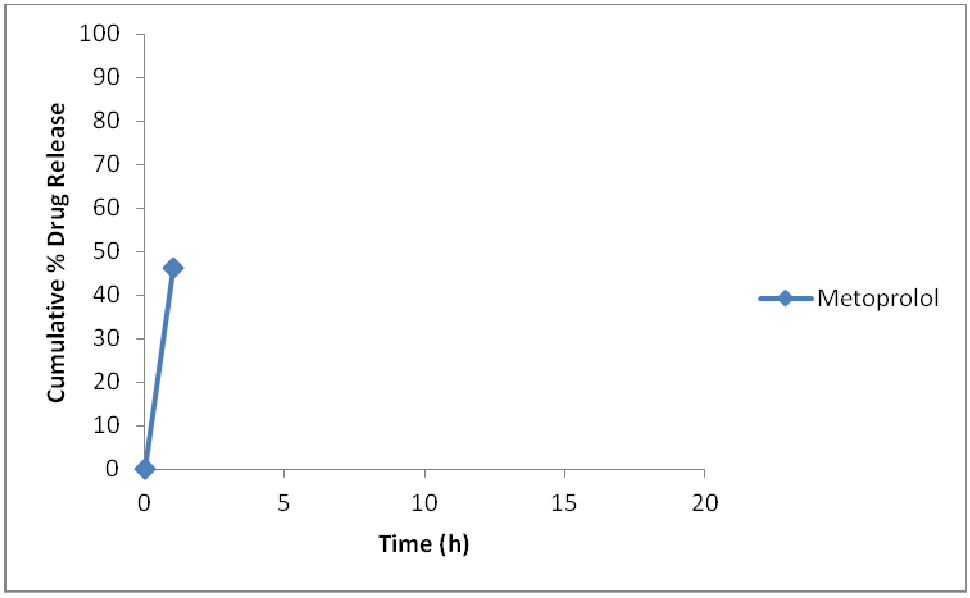



**Fig: 1 *In vitro* dissolution profile of formulation F- 1**

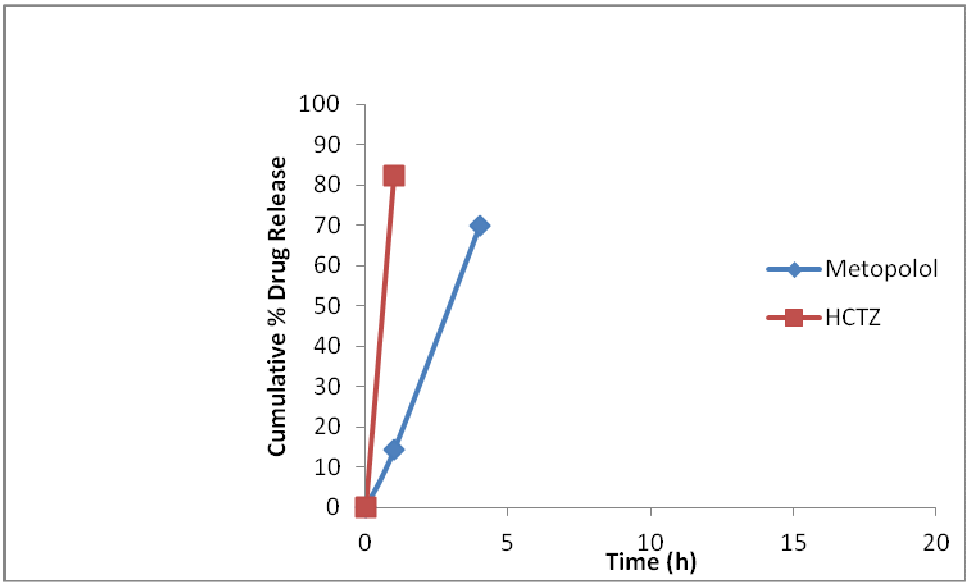



**Fig: 2 *In vitro* dissolution profile of formulation F2**

***In vitro dissolution profile of Bilayer tablet* F-3**

| **Sustained release layer of Metoprolol succinate** | | | | |
|---|---|---|---|---|
| **Sl. No** | **Time ( hr)** | **Limit (%)** | **Amount of drug release (mg)** | **Cumulative % drug release*** |
| 1. | 1 | NMT 25% | 3.11 | 12.45±0.02 |
| 2. | 4 | 20 - 40 | 8.84 | 35.35±0.04 |
| 3. | 8 | 40 - 60 | 17.08 | 68.34±0.05 |
| 4. | 20 | NLT 80% | -- | --- |
| **Immediate release layer of Hydrochlorothiazide** | | | | |
| **Sl. No** | **Time (hr)** | **Limit (%)** | **Amount of the drug (mg)** | **Cumulative % drug release*** |
| 1. | 1.0 | NLT 60% | 10.72 | 85.72±0.03 |

***all the values are mean ±RSD, n=6**

In the above table gives the *in vitro* dissolution profile of Metoprolol succinate sustained release and Hydrochlorothiazide immediate release tablet for the formulation F-3. The drug release of Metoprolol succinate at 8$^{th}$ hour drug release was obtained from above limit.

The release of Hydrochlorothiazide at the end of 1$^{st}$ hour was found to be 85.72%.

In the below Fig: 3 shows the graph of *in vitro* drug release profile of sustained release of Metoprolol succinate and immediate release of Hydrochlorothiazide for the formulation F-3.

*In vitro dissolution profile of Bilayer tablet* **F-4**

| **Sustained release layer of Metoprolol succinate** | | | | |
|---|---|---|---|---|
| **Sl. No** | **Time (hr)** | **Limit(%)** | **Amount of drug release (mg)** | **Cumulative % drug release*** |
| 1. | 1 | NMT 25% | 3.59 | 14.35±0.02 |
| 2. | 4 | 20 – 40 | 8.67 | 34.7±0.04 |
| 3. | 8 | 40 – 60 | 18.16 | 72.65±0.5 |
| 4. | 20 | NLT 80% | -- | -- |
| **Immediate release layer of Hydrochlorothiazide** | | | | |
| **Sl. No** | **Time (hr)** | **Limit (%)** | **Amount of drug release (mg)** | **Cumulative % drug release** |
| 1. | 1.0 | NLT 60% | 11.19 | 89.5±0.6 |

***all the values are mean ±RSD, n=6**

In the above table gives the *in vitro* dissolution profile of Metoprolol succinate sustained release and Hydrochlorothiazide immediate release tablet for the formulation F-4. The drug release in this formulation at 1$^{st}$, 4$^{th}$ hour release was regulated and 8$^{th}$ hour release was above the limit.

The release of Hydrochlorothiazide at the end of the 1$^{st}$ hour was found to be 89.50%.

In the below Fig: 4 shows the graph of *in vitro* drug release profile of sustained release of Metoprolol succinate and immediate release of Hydrochlorothiazide for the formulation F-4.

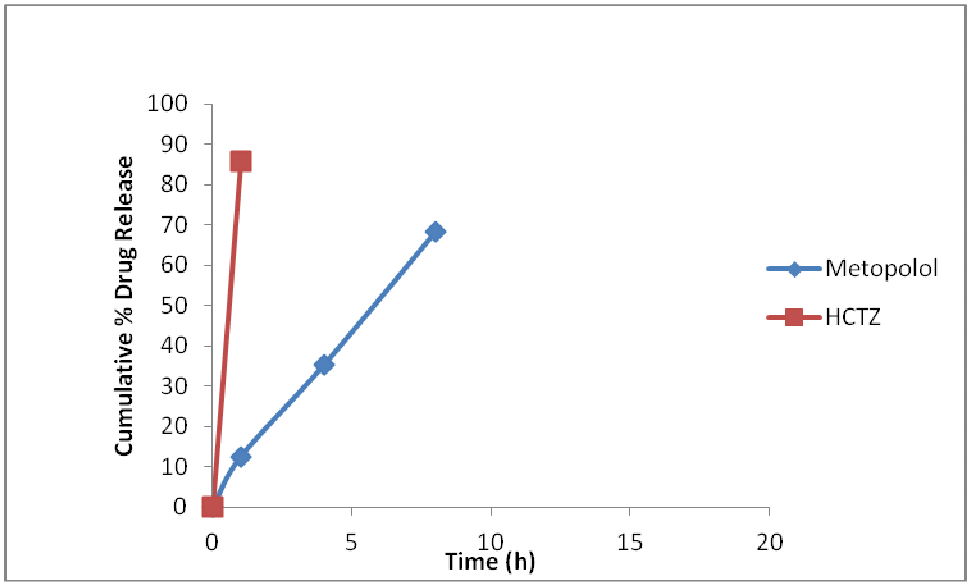



**Fig: 3 *In vitro* dissolution profile of formulation F- 3**

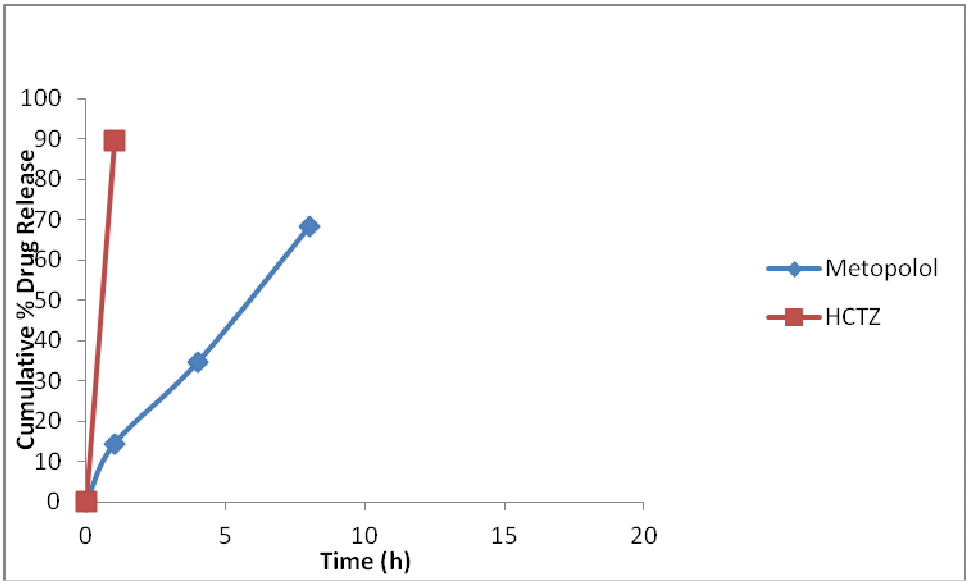



**Fig: 4 *In vitro* dissolution profile of formulation F- 4**

***In vitro dissolution profile of Bilayer tablet* F-5**

| **Sustained release layer of Metoprolol succinate** | | | | |
|---|---|---|---|---|
| **Sl. No** | **Time (hr)** | **Limit (%)** | **Amount of drug release (mg)** | **Cumulative % drug release*** |
| 1. | 1 | NMT 25% | 3.81 | 15.24±0.03 |
| 2. | 4 | 20 – 40 | 11.66 | 46.66±0.05 |
| 3. | 8 | 40 – 60 | -- | -- |
| 4. | 20 | NLT 80% | -- | -- |
| **Immediate release layer of Hydrochlorothiazide** | | | | |
| **Sl. No** | **Time (hr)** | **Limit (%)** | **Amount of drug release (mg)** | **Cumulative % drug release*** |
| 1. | 1.0 | NLT 60% | 11.02 | 95.4±0.7 |

***all the values are mean ±RSD, n=6**

In formulation F-1 to F-5 the SR layer consists of HPMC K100M and HPMC K4M in the concentration of 20% to 50% and 2% to 5% with respect to the average weight and the weight of the tablet was balanced with Micro crystalline cellulose PH101. The release of the drug in F-1 to F-5 was not found to be within the internal specification limit. Therefore the release of the drug was more than the limit. The drug release at 4$^{th}$ hour was crossing the lmit.

In the formulation F-2, F-3, F-4 and F-5 starch plain was used as a binder in the concentration of 4% to 12% and lubricant concentration is 0.4 to 0.8% respectively to meet the compression and dissolution profile of Hydrochlorothiazide with the specification limit. At the end of 60 min, the release profile of Hydrochlorothiazide in the formulation F-2, F-3, F-4 and F-5 was found to 82.33%, 85.72%, 89.50% and 95.4%

respectively. Among these four trials F-5 was found to be satisfactory and it was selected as an immediate release layer to formulate with the sustained release layer of Metoprolol Succinate as a Bilayer tablet.

In the below Fig: 5 shows the graph of *in vitro* drug release profile of sustained release of Metoprolol succinate and immediate release of Hydrochlorothiazide for the formulation F-5.

***In vitro dissolution profile of Bilayer tablet*** **F-6**

| **Sustained release layer of Metoprolol succinate** | | | | |
|---|---|---|---|---|
| **Sl. No** | **Time (hr)** | **Limit (%)** | **Amount of drug release (mg)** | **Cumulative % drug release*** |
| 1. | 1 | NMT 25% | 2.34 | 9.35±0.05 |
| 2. | 4 | 20 – 40 | 9.61 | 42.45±0.04 |
| 3. | 8 | 40 – 60 | 11.70 | 62.8±0.18 |
| 4. | 20 | NLT 80% | 20.17 | 92.65±0.6 |
| **Immediate release layer of Hydrochlorothiazide** | | | | |
| **Sl. No** | **Time (hr)** | **Limit (%)** | **Amount of drug release (mg)** | **Cumulative % drug release*** |
| 1. | 1.0 | NLT 60% | 11.6 | 95.4±0.6 |

***all the values are mean ±RSD, n=6**

In order to retard the release of the drug, the polymer HPMC K100 concentration was increased to 51.67% (26.67% intra granulation and 25%extra granulation) and HPMC K4M concentration was increased to 3.33% (1.67% intra granulation and 1.67% extra granulation) in formulation F-6. But the release of the drug at $4^{th}$ and $8^{th}$ hour was

42.45% and 62.8% higher to the desired release pattern.The drug release at and 1st and 20th hour was controlled the release and 4th and 8th hour was above the limit.

The release of the Hydrochlorothiazide at the end of the 1st hour was found to be 95.40%.

In the below Fig: 6 shows the graph of *in vitro* drug release profile of sustained release of Metoprolol succinate and immediate release of Hydrochlorothiazide for the formulation F-6.

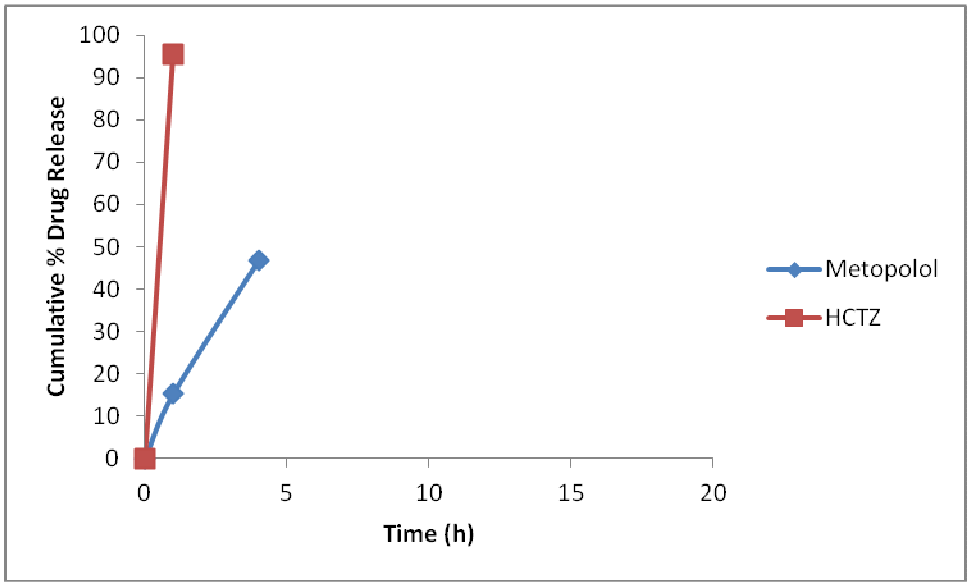



**Fig: 5 *In vitro* dissolution profile of formulation F- 5**

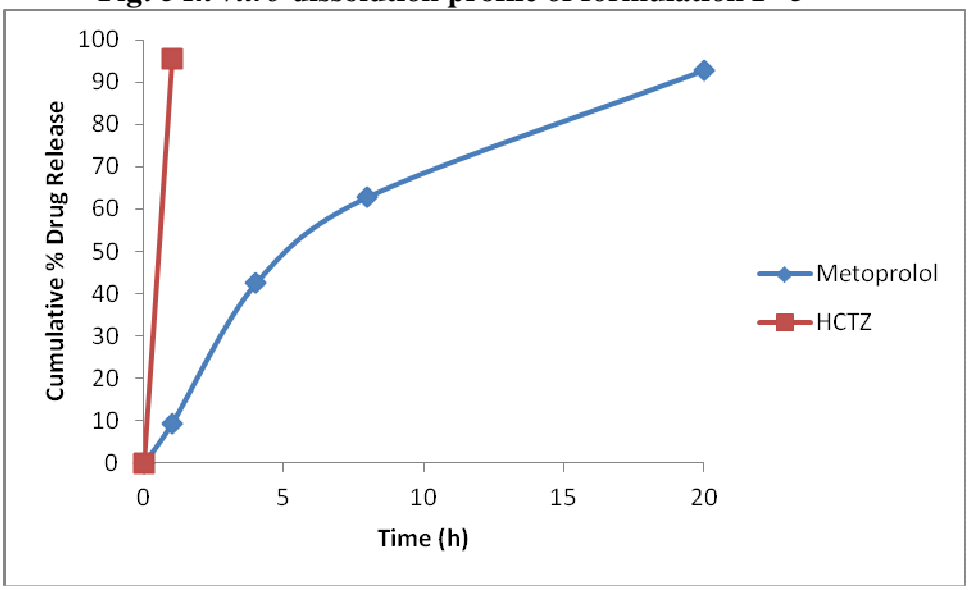



**Fig: 6 *In vitro* dissolution profile of formulation F- 6**

***In vitro dissolution profile of Bilayer tablet* F-7**

| **Sustained release layer of Metoprolol succinate** | | | | |
|---|---|---|---|---|
| **Sl. No** | **Time (hr)** | **Limit (%)** | **Amount of drug release (mg)** | **Cumulative % drug release*** |
| 1. | 1 | NMT 25% | 4.07 | 17.34±0.13 |
| 2. | 4 | 20 – 40 | 7.69 | 33.06±0.6 |
| 3. | 8 | 40 – 60 | 12.85 | 55.35±0.8 |
| 4. | 20 | NLT 80% | 22.72 | 97.78±0.16 |
| **Immediate release layer of Hydrochlorothiazide** | | | | |
| **Sl. No** | **Time (hr)** | **Limit (%)** | **Amount of drug release (mg)** | **Cumulative % drug release*** |
| 1. | 1 | NLT 60% | 11.91 | 95.29±0.5 |

***all the values are mean ±RSD, n=6**

In the above table gives the *in vitro* dissolution profile of Metoprolol succinate sustained release and Hydrochlorothiazide immediate release tablet for the formulation F-7 to increase the release of the drug, the concentration of HPMC K100M was increased to 1.5% was found to be satisfactory where the drug release of Metoprolol succinate at 1$^{st}$, 4$^{th}$, 8th and 20$^{th}$ hour was found to be, 17.34, 33.06, 55.35, and 97.78% respectively.

The release of Hydrochlorothiazide at the end of 1 hour was found to be 95.29%.

In the below Fig: 7 shows the graph of *in vitro* drug release profile of sustained release of Metoprolol succinate and immediate release of Hydrochlorothiazide for the formulation F-7.

***In vitro dissolution profile of Bilayer tablet* F-8**

| **Sustained release layer of Metoprolol succinate** | | | | |
|---|---|---|---|---|
| **Sl. No** | **Time (hr)** | **Limit (%)** | **Amount of drug release (mg)** | **Cumulative % drug release*** |
| 1. | 1 | NMT 25% | 4.32 | 17.29±0.13 |
| 2. | 4 | 20 – 40 | 8.40 | 33.62±0.6 |
| 3. | 8 | 40 – 60 | 12.68 | 54.71±0.8 |
| 4. | 20 | NLT 80% | 22.48 | 97.92±0.16 |
| **Immediate release layer of Hydrochlorothiazide** | | | | |
| **Sl. No** | **Time (hr)** | **Limit (%)** | **Amount of drug release (mg)** | **Cumulative % drug release*** |
| 1. | 1.0 | NLT 60% | 11.90 | 95.28±0.3 |

***all the values are mean ±RSD, n=6**

In the above table gives the *in vitro* dissolution profile of Metoprolol succinate sustained release and Hydrochlorothiazide immediate release tablet for the formulation F-8. The drug release at 1$^{st}$, 4$^{th}$, 8$^{th}$ and 20$^{th}$ hour was found to be 17.29, 33.62, 54.71 and 97.92% respectively.

The drug release of the Hydrochlorothiazide at 1$^{st}$ hour was found to be 95.28%.

In the below Fig: 8 shows the graph of *in vitro* drug release profile of sustained release of Metoprolol succinate and immediate release of Hydrochlorothiazide for the formulation F-8.

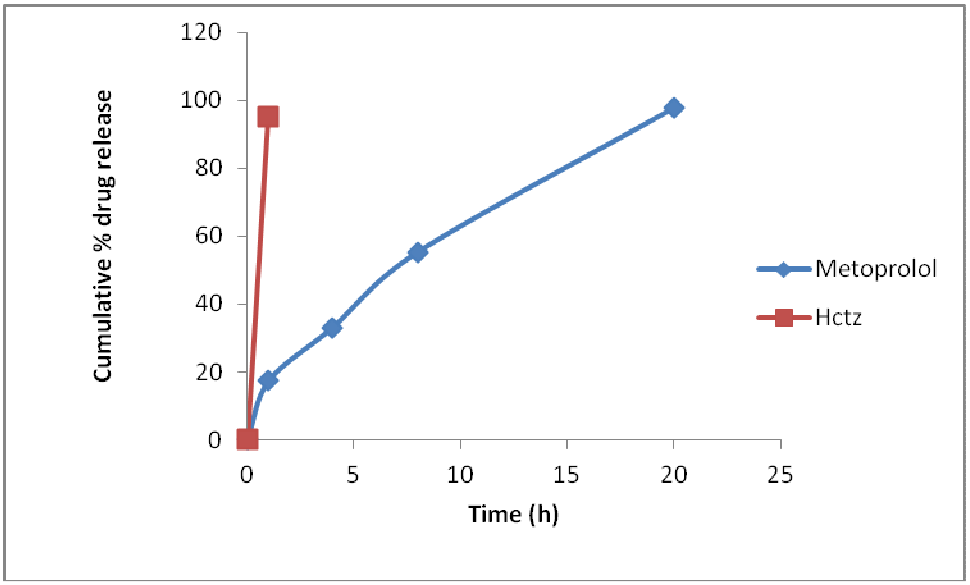



**Fig: 7 *In vitro* dissolution profile of formulation F- 7**

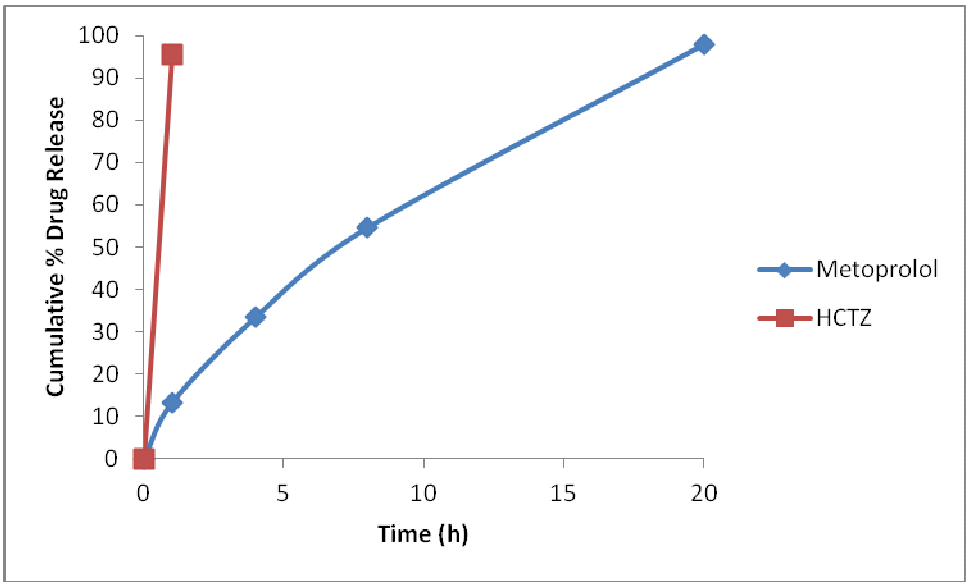



**Fig: 8 *In vitro* dissolution profile of formulation F-8**

***In vitro dissolution profile of Bilayer tablet* F-9**

| **Sustained release layer of Metoprolol succinate** | | | | |
|---|---|---|---|---|
| **Sl. No** | **Time (hr)** | **Limit (%)** | **Amount of drug release (mg)** | **Cumulative % drug release*** |
| 1. | 1 | NMT 25% | 3.33 | 17.3±0.13 |
| 2. | 4 | 20 – 40 | 7.39 | 33.59±0.6 |
| 3. | 8 | 40 – 60 | 12.7 | 55.80±0.6 |
| 4. | 20 | NLT 80% | 22.47 | 97.96±0.8 |
| **Immediate release layer of Hydrochlorothiazide** | | | | |
| **Sl. No** | **Time (hr)** | **Limit (%)** | **Amount of drug release (mg)** | **Cumulative % drug release*** |
| 1. | 1.0 | NLT 60% | 11.91 | 95.2±0.3 |

***all the values are mean ±RSD, n=6**

In the above table gives the *in vitro* dissolution profile of Metoprolol succinate sustained release and Hydrochlorothiazide immediate release tablet for the formulation F-9. The drug release at 1$^{st}$, 4$^{th}$, 8$^{th}$ and 20$^{th}$ hour was found to be 17.3, 33.59, 55.80, and 97.96% respectively.

The release of Hydrochlorothiazide at 1$^{st}$ hour was found to be 95.2%.

In the below Fig: 9 shows the graph of *in vitro* drug release profile of sustained release of Metoprolol succinate and immediate release of Hydrochlorothiazide for the formulation F-9.

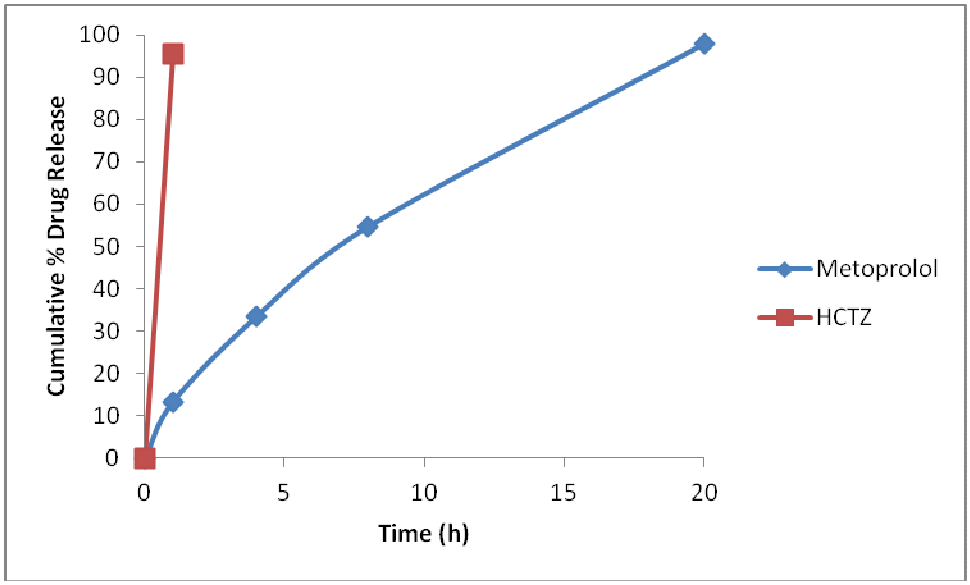



**Fig: 9 *In vitro* dissolution profile of formulation F-9**

All the batches of Bilayer tablets fulfilled the official requirements of uniformity of dosage units. The average percentage deviation of 20 tablets of each formula was less than ± 4%. The thickness and hardness of the tablet ranged from 4.5–4.7mm and 9 - 10.5kg/cm$^2$ respectively. The percentage friability of all batches ranged from 0.11 to 0.34%w/w. The drug content was found to be ranged from 92.65% to 97.8% for Metoprolol Succinate and 82.33% to 95.28% for Hydrochlorothiazide.

**Formulation development of Bilayer tablet**

The formulation consists of two layers sustained release layer of Metoprolol Succinate and immediate release layer of Hydrochlorothiazide. Development trials of about 5000 tablets were taken and evaluated the pre compression and post compression parameters of Bilayer tablets.

Precompressional parameters of Bilayer tablets (bulk density, tapped density, Carr's index, Hausner's ratio and angle of repose) are in the range of given in official standard, indicated that granules prepared by wet granulation method were free flowing. The postcompressional parameters of Bilayer tablets (hardness, friability, weight variation, thickness and drug content) were within the acceptable limits. The optimized bilayered

tablets were selected for FTIR studies and DSC studies did not show any interaction between the drug, polymer and excipients.

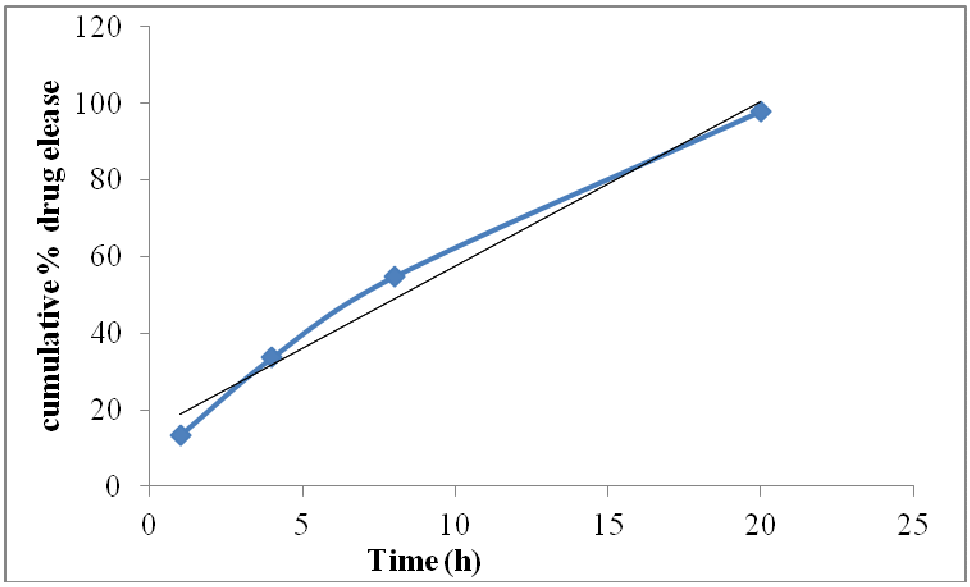



**Fig: 10 Zero order kinetics**

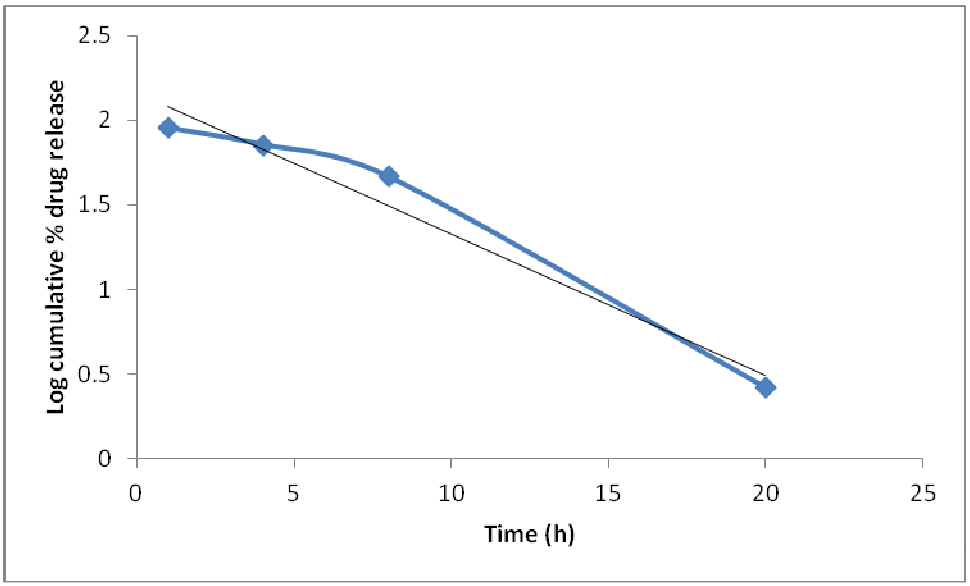



**Fig: 11 first order kinetics**

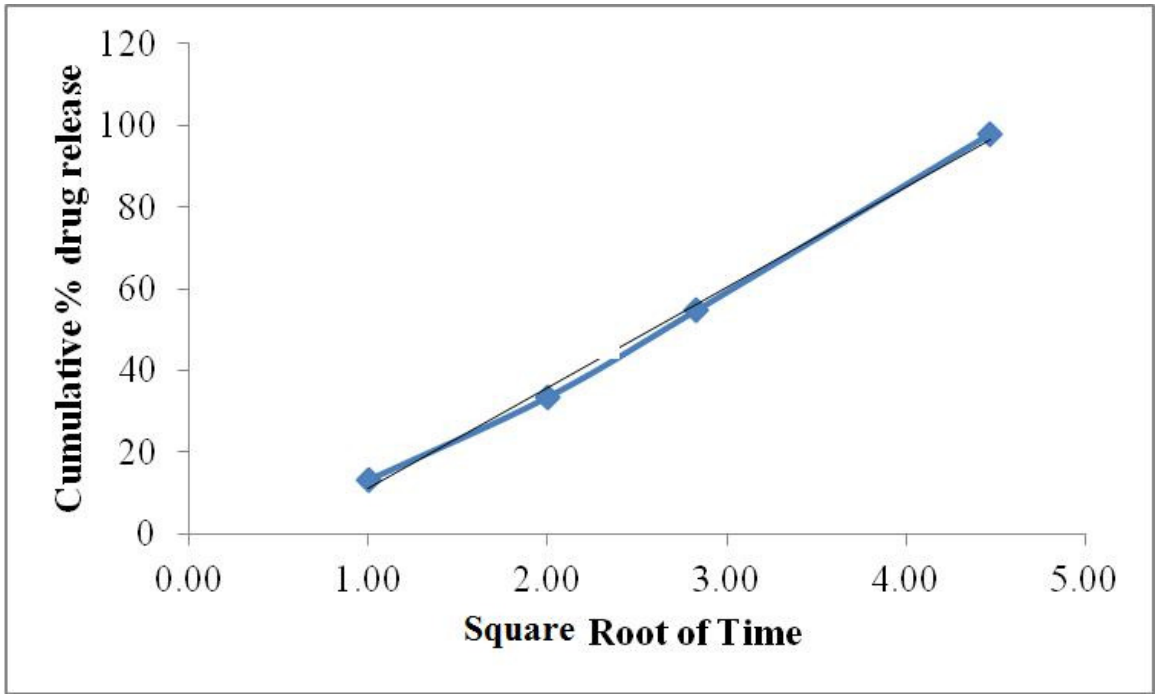



**Fig: 12 Higuchi diffusion kinetics**

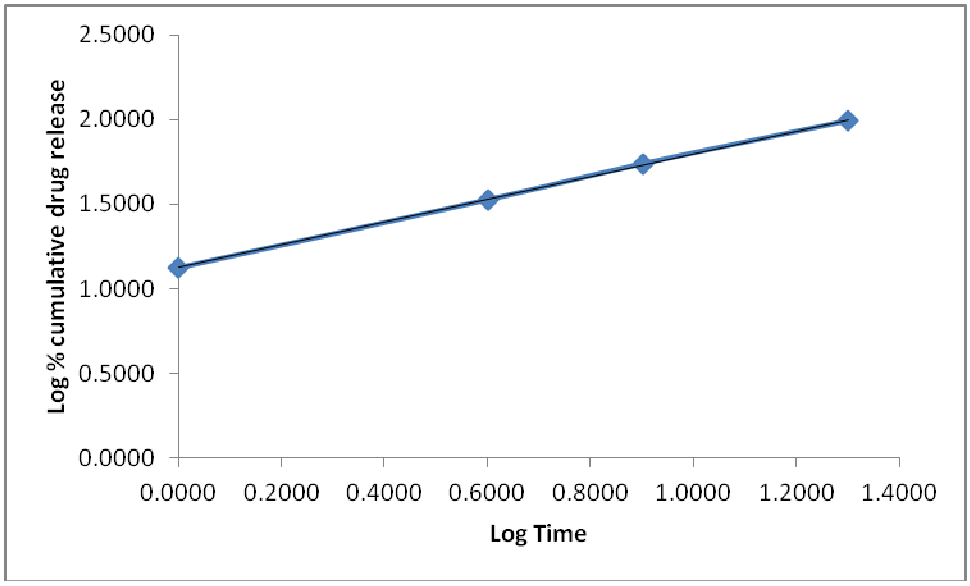



**Fig: 13 Korsmeyer-Peppas equation**

**Table: 7.5 Kinetics studies of Bilayer tablets**

| Release kinetics | $R^2$ |
|---|---|
| **Zero order** | 0.981 |
| **First order** | 0.966 |
| **Higuchi** | 0.996 |
| **Korsmeyer-peppas** | 0.998 |

**Release kinetics study for optimized Bilayer tablet:**

The kinetics of drug release was determined based on korsmeyer-peppas equation obtained by *in vitro* dissolution data to various kinetics models.

Accordingly the $R^2$ value was found to 0.981 for zero order, 0.966 for first order, 0.996 for Higuchi, 0.998 for korsmeyer-peppas plot. The $R^2$ value of korsemeyer-peppas was close to 1 and n value was found to be 1.4.

Hence the release kinetics was fitted to korsemeyer-peppas equeation follows non-fickian diffusion model, and the mechanism of drug release is regarded as super case II transport.

**Evaluation of Metoprolol Succinate Layer –I (SR) and Hydrochlorothiazide Layer-II (IR)**

Bulk density and tapped density for Metoprolol Succinate sustained release granules were found to be between 0.648 to 0.668 and 0.728 to 0.778 respectively. Carr's index and Hausner's ratio were obtained in the range of 11.82 to 14.51 and 1.13 to 1.17 respectively. Angle of repose was observed in the range of 25°11´ to 27°84´. Moisture content was found to be between 2.0 to 2.5. The results showed in the Table No: 7.7 indicate good flow property and compressibility.

Bulk density and Tapped density for Hydrochlorothiazide IR granules were found to be between 0.593 to 0.640 and 0.720 to 0.771 respectively. Carr's index and Hausner ratio were obtained in the range of 11.11 to 19.32 and 1.13 to 1.24 respectively. Angle of repose was observed between 27°69´ to 33°70´. The results showed in the Table No: 7.6 indicate that the granules possessed good flow property and compressibility.

**7.8 Stability studies:**

**Table: 7.8.1 *In vitro* dissolution profile of Bilayer tablet F-8 after stability study at 40ºCº±2ºC/75%±5%RH after 30 days:**

| Sustained release layer of Metoprolol succinate | | | | |
|---|---|---|---|---|
| **Sl. No** | **Time (hr)** | **Limit (%)** | **Amount of drug release (mg)** | **Cumulative % drug release** |
| 1. | 1 | NMT 25% | 4.06 | 17.30±0.04 |
| 2. | 4 | 20 – 40 | 7..64 | 33.04±0.03 |
| 3. | 8 | 40 – 60 | 12.84 | 55.68±0.05 |
| 4. | 20 | NLT 80% | 22.71 | 97.76±0.03 |
| **Immediate release layer of Hydrochlorothiazide** | | | | |
| **Sl. No** | **Time (hr)** | **Limit (%)** | **Amount of drug release (mg)** | **Cumulative %drug release** |
| 1. | 1.0 | NLT 60% | 11.91 | 95.28±0.01 |

In the above table gives the *in vitro* dissolution profile of formulation F- 8 after stability study at $40^0$C±$2^0$C /75%±5% RH after 30 days. The drug release of Metoprolol Succinate at $1^{st}$, $4^{th}$, $8^{th}$ and $20^{th}$ h was found to be 17.30%, 33.04%, 55.68% and 97.76% respectively.

The release of Hydrochlorothiazide at the end of 1hr was found to be 95.28 %.

Fig: 16 show the graph of *in vitro* drug release profile of formulation F- 8 after stability study at $40^0$C±$2^0$C /75%±5% RH after 30 days.

**Table: 7.8.2 *In vitro* dissolution profile of Bilayer tablet F- 9 after stability study at $40^0$C±$2^0$C /75%±5%RH after 30 days**

| Sustained release layer of Metoprolol Succinate | | | | |
|---|---|---|---|---|
| **Sl. No** | **Time (h)** | **Limit (%)** | **Amount of drug release (mg)** | **Cumulative % drug release** |
| 1. | 1 | NMT 25 | 4.06 | 17.32± 0.1 |
| 2. | 4 | 20-40 | 7.68 | 33.04± 0.03 |
| 3. | 8 | 40-60 | 12.83 | 55.34 ± 0.03 |
| 4. | 20 | NLT 80 | 22.71 | 97.76±0.03 |
| **Immediate release layer of Hydrochlorothiazide** | | | | |
| **Sl. No** | **Time (h)** | **Limit (%)** | **Amount of drug release (mg)** | **Cumulative % drug release** |
| 1. | 1 hr | NLT 60% | 11.89 | 95.12 ±0.01 |

In the above table gives the *in vitro* dissolution profile of formulation F- 9 after stability study at $40^0$C±$2^0$C /75%±5% RH after 30 days. The drug release of Metoprolol Succinate at $1^{st}$, $4^{th}$, $8^{th}$ and $20^{th}$ h was found to be 17.32%, 33.04%, 55.34% and 97.76% respectively.

The release of Hydrochlorothiazide at the end of 1hr was found to be 95.12 %.

Fig: 17 show the graph of *in vitro* drug release profile of formulation F- 9 after stability study at $40^0$C±$2^0$C /75%±5% RH after 30 days.

**Table: 7.8.3 *In vitro* dissolution profile of Bilayer tablet F-8 after stability study at 40ºCº±2ºC/75%±5%RH after 60 days:**

| **Sustained release layer of Metoprolol succinate** | | | | |
|---|---|---|---|---|
| **Sl. No** | **Time (hr)** | **Limit (%)** | **Amount of drug release (mg)** | **Cumulative % drug release** |
| 1. | 1 | NMT 25% | 4.04 | 17.33±0.04 |
| 2. | 4 | 20 – 40 | 7.05 | 32.72±0.03 |
| 3. | 8 | 40 – 60 | 12.78 | 55.30±0.04 |
| 4. | 20 | NLT 80% | 22.69 | 97.64±0.03 |
| **Immediate release layer of Hydrochlorothiazide** | | | | |
| **Sl. No** | **Time (hr)** | **Limit (%)** | **Amount of drug release (mg)** | **Cumulative % drug release** |
| 1. | 1.0 | NLT 60% | 11.89 | 95.19±0.01 |

In the above table gives the *in vitro* dissolution profile of formulation F- 8 after stability study at $40^0$C±$2^0$C /75%±5% RH after 60 days. The drug release of Metoprolol Succinate at 1st, 4th, 8th and 20th h was found to be 17.33%, 32.72%, 55.30% and 97.64% respectively.

The release of Hydrochlorothiazide at the end of 1hr was found to be 95.19 %.

Fig: 18 show the graph of *in vitro* drug release profile of formulation F- 8 after stability study at $40^0$C±$2^0$C /75%±5% RH after 60 days.

**Table: 7.8.4 *In vitro* dissolution profile of Bilayer tablet F-9 after stability study at 40ºCº±2ºC/75%±5%RH after 60 days:**

| Sustained release layer of Metoprolol succinate | | | | |
|---|---|---|---|---|
| **Sl. No** | **Time (hr)** | **Limit (%)** | **Amount of drug release (mg)** | **Cumulative % drug release** |
| 1. | 1 | NMT 25% | 4.05 | 17.22±0.1 |
| 2. | 4 | 20 – 40 | 7.59 | 33.05±0.03 |
| 3. | 8 | 40 – 60 | 12.75 | 55.28±0.03 |
| 4. | 20 | NLT 80% | 22.71 | 97.61±0.03 |
| **Immediate release layer of Hydrochlorothiazide** | | | | |
| **Sl. No** | **Time (hr)** | **Limit (%)** | **Amount of drug release (mg)** | **Cumulative % drug release** |
| 1. | 1.0 | NLT 60% | 11.70 | 95.23±0.01 |

In the above table gives the *in vitro* dissolution profile of formulation F- 9 after stability study at $40^0$C±$2^0$C /75%±5% RH after 60 days. The drug release of Metoprolol Succinate at $1^{st}$, $4^{th}$, $8^{th}$ and $20^{th}$ hr was found to be 17.22%, 33.05%, 55.28% and 97.61% respectively.

The release of Hydrochlorothiazide at the end of 1hr was found to be 95.23 %.

Fig: 19 show the graph of *in vitro* drug release profile of formulation F- 9 after stability study at $40^0$C±$2^0$C /75%±5% RH after 60 days.

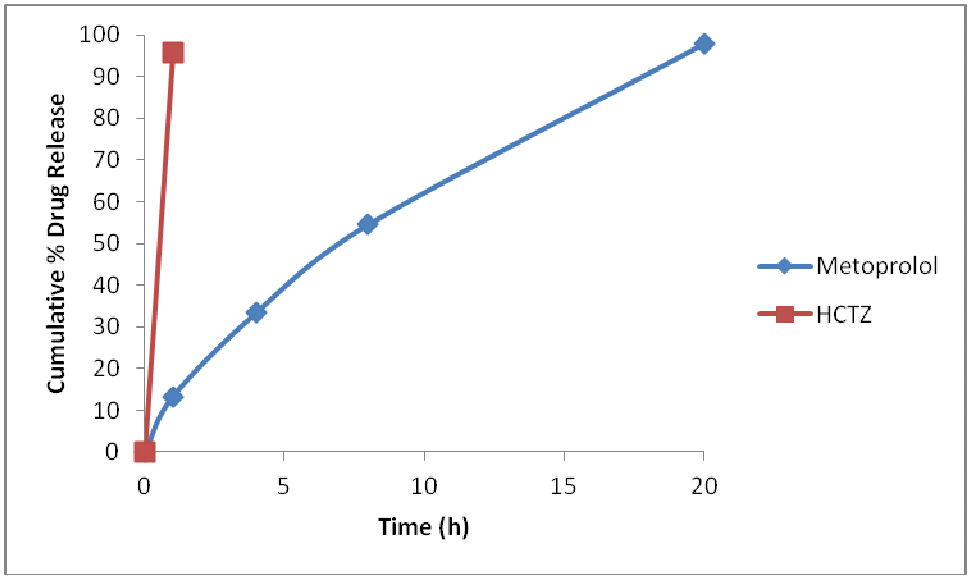



**Fig:16 *In vitro* dissolution profile of formulation F- 8 after stability study at $40^0C \pm 2^0C$ /75%±5% RH after 30 days**

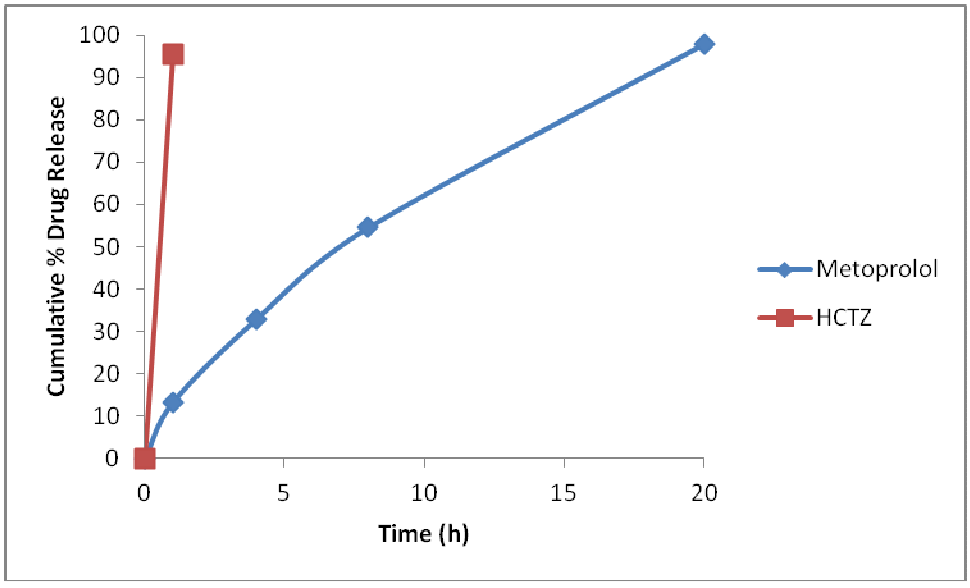



**Fig :17 *In vitro* dissolution profile of formulation F- 9 after stability study at $40^0C \pm 2^0C$ /75%±5% RH after 30 days**

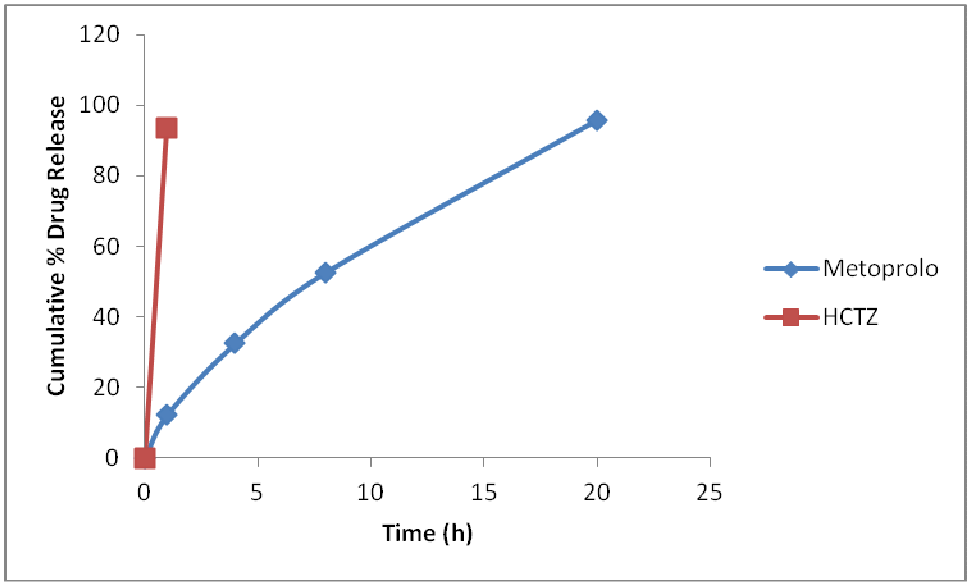



**Fig: 18** ***In vitro*** **dissolution profile of formulation F- 8 after stability study at $40^0C \pm 2^0C$ /75%±5% RH after 60 days**

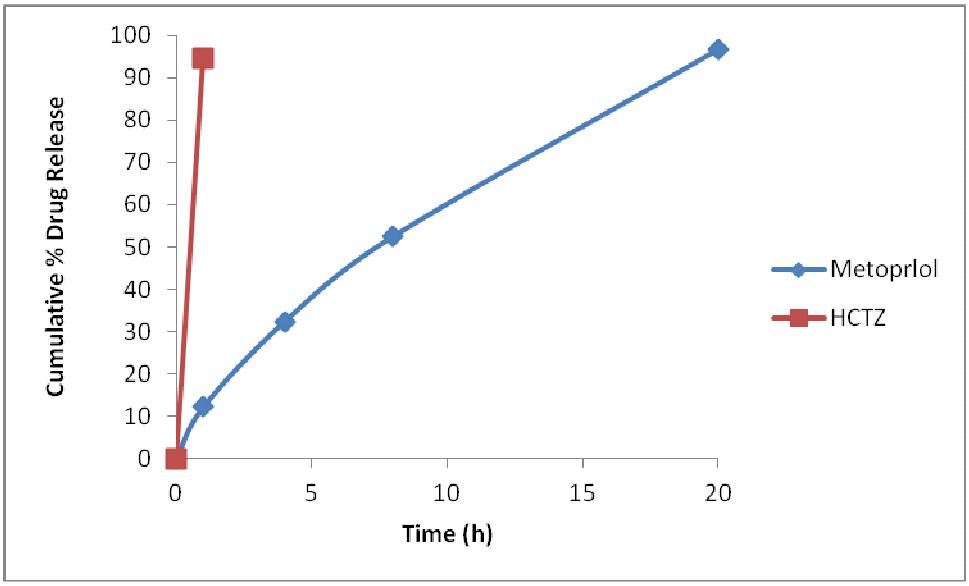



**Fig: 19** ***In vitro*** **dissolution profile of formulation F- 9 after stability study at $40^0C \pm 2^0C$ /75%±5% RH after 60 days**

**Reproducibility of batch:**

To check the reproducibility of batch, another batch (F-8, and F-9) was prepared with the same formula of F- 7. The drug release at $1^{st}$, $4^{th}$, $8^{th}$ and $20^{th}$ h was found to be 17.34%, 33.59%, 55.80% and 97.96% for Metoprolol Succinate and 95.2%for Hydrochlorothiazide at 1 hr. Hence, the drug release of reproducibility batch (F-9) was observed similar to the optimized batch (F-7).

**Stability batch:**

Stability studies were conducted for the formulation F- 8 and F- 9. The stability study was performed at 40°C±2°C/75%RH±5%Rh for a specific time period. The tablets were analyzed for appearance, weight variation, drug content and *in vitro* drug release. The overall results showed that the formulation is stable at the above mentioned storage conditions and were not altered significantly on storage indicating good stability.

**Table: 7.9 Evalution of Bilayer tablets of Metoprolol succinate sustained release and Hydrochlorothiazide immediate release after stability study at 40ºC±2ºC/75%±5%RH**

| S.No | Tests | Specifications | 1 Month | | 2 Month | |
|---|---|---|---|---|---|---|
| 1. | Description | Blue / White colored circular shaped uncoated Bilayer tablet | F – 8 Complies | F – 9 Complies | F – 8 Complies | F – 9 Complies |
| 2. | Average weight (mg) | 375±3% | 375±3% | 375±2% | 375±2% | 374±2% |
| 3. | Thickness (mm) | 4.80±0.2 | 4.80±0.24 | 4.80±0.24 | 4.85±2% | 4.80±4% |
| 4. | Hardness (kg/cm2) | NLT 3.0 | 6.5±0.02 | 6.5±0.02 | 6.5±4% | 6.5±6% |
| 5. | Friability (% w/w) | NMT 1% | 0.22±0.01 | 0.22±0.01 | 0.28±1% | 0.31±1% |
| 6. | Weight variation (n=20) | ±5% from the average weight | ±3.8 | ±3.8 | ±4.1 | ±3.9 |
| 7. | Assay | | | | | |
| | a) Metoprolol succinate equivalent to Metoprolol tartarate | 90 – 110% | 93.6 | 95.2 | 93.2 | 95.0 |
| | b) Hydrochlorothiazide | 90 – 110% | 95.6 | 94.4 | 95.1 | 94.1 |

**F-8 and F-9 batches are taken with same bill of materials as F-7.**

**7.10 FT - IR Studies:**

In the figure shows the FT-IR spectra of plain Metoprolol Succinate, plain Hydrochlorothiazide, combination of Metoprolol Succinate and Hydrochlorothiazide and optimized formulation.

IR spectra of pure Metoprolol Succinate Showed the major bands at 1615$cm^{-1}$, 1568 $cm^{-1}$ for aromatic C=C streching, 2259 $cm^{-1}$, 2877 $cm^{-1}$ for aliphatic C-H stretching, 1072 $cm^{-1}$ for C=O stretching.

IR spectra of pure Hydrochlorothiazide showed the major bands at 1601$cm^{-1}$ ,1604 $cm^{-1}$ C=C for aromatic carbon stretching for $So_2$ 1335 $cm^{-1}$, 1151 $cm^{-1}$ and 3393 $cm^{-1}$ , 3363 $cm^{-1}$ for N-H and the C-H stretching in aliphatic ring at 2851$cm^{-1}$, 2925 $cm^{-1}$

The results of IR spectra of active ingredients and excipients also revealed that there was no considerable change in the peaks was observed in bands of Metoprolol Succinate and Hydrochlorothiazide, hence there is no interaction between the drug, polymer and excipients used in the tablet.

**7.11 DSC Studies:**

DSC curves showed that there was no any incompatibility between Metoprolol succinate and Hydrochlorothiazide. In the combination DSC, one peak was obtained at 141.60°C for Metoprolol succinate and another at 272.50 °C for Hydrochlorothiazide. In the individual DSC studies of the drugs, Metoprolol succinate peak was obtained at 138.65 °C and Hydrchlorothiazide peak at 29.53°C. These peaks match the peaks reported in the literature for pure drugs.

## Conclusion

The present research was carried out to develop a bilayer tablet of Metoprolol Succinate using hydrophilic matrix formers such as HPMC K100M and HPMC K4M for the sustained release layer. Starch is used as a binder for immediate release layer of Hydrochlorothiazide.

Combination of Metoprolol Succinate and Hydrochlorothiazide are indicated for the treatment and relief of Antihypertensive agent

Tablet formulation (F-7) showed acceptable pharmacotechnical properties and complied with the internal specification for weight variation, thickness, hardness, friability, drug content and *in vitro* drug release. Drug release from the matrix was found to decrease with increase in polymer concentration in intra and extra granulation, where the polymer concentration was employed from 20-50%w/w of the average tablet weight. However, HPMC 4M required to channelize the drug release was optimized with 2% to 5%. Similarly starch with 12%w/w optimized from 4% onwards, as binder to compress IR layer and dissolution within 60 minutes (internal specification).

Reproducibility was checked by intra batch variability study and found no pronounced variation was observed.

The optimized bilayered tablets followed Korsmeyer-peppas kinetic and showed no significant change in physical appearance, drug content or *in vitro* dissolution pattern after storage at 40°C/75%RH for 2 months. Hence, it is finally concluded that, the Bilayer tablet technology can be successfully applied for sustained release of Metoprolol Succinate and immediate-release of Hydrochlorothiazide.

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